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College of Science

Department of Biology

Infectious disease

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طلبه الدراسات العليا الدكتوراه

الفصل الدراسي الأول

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Lect. 1 Principles of bacterial infectious disease

Infection is the invasion of a host organism's body tissues by disease-causing agents,

their multiplication, and the reaction of host tissues to these organisms and

the toxins they produce.[1] **Infectious diseases**, also known as **transmissible**

diseases or **communicable diseases**, comprise clinically evident illness (i.e.,

characteristic medical signs and/or symptoms of disease) resulting from the **infection**,

presence and growth of pathogenic biological agents in an individual host organism.

Infections are caused by infectious agents such

as viruses, viroids,and prions, microorganisms such as bacteria, nematodes such

As roundworms and pinworms, arthropods such as ticks, mites, fleas,

and lice, fungi such as ringworm, and other macroparasites such as tapeworms.

Hosts can fight infections using their immune system. Mammalian hosts react to

infections with an innate response, often involvingin flammation, followed by an adaptive response.[2]

The branch of medicine that focuses on infections and pathogens is *infectious disease*

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infections (antibiotics, antivirals, antifungals, antiprotozoals, antihelminthics). Bacterial

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Symptomatic infections are *apparent,* whereas an infection that is active but does not

produce noticeable symptoms may be called *inapparent, silent,* or *subclinical.* An infection that is inactive or dormant is called a *latent infection*.[3]

A short-term infection is an *acute* infection. A long-term infection is a chronic infection

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Primary versus opportunistic

Among the vast varieties of microorganisms, relatively few cause disease in otherwise

healthy individuals.[4] Infectious disease results from the interplay between those few pathogens and the defenses of the hosts they infect. The appearance and severity of disease resulting from any pathogen, depends upon the ability of that pathogen to damage the host as well as the ability of the host to resist the pathogen. Clinicians therefore classify infectious microorganisms or microbes according to the status of host defenses - either as *primary pathogens* or as *opportunistic pathogens*:

Primary pathogens cause disease as a result of their presence or activity within the normal, healthy host, and their intrinsic virulence (the severity of the disease they cause) is, in part, a necessary consequence of their need to reproduce and spread. Many of the most common primary pathogens of humans only infect humans, however many serious diseases are caused by organisms acquired from the environment or which infect non-human hosts.

Opportunistic pathogens

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The symptoms of an infection depend on the type of disease. Some signs of infection affect the whole body generally, such as fatigue, loss of appetite, weight loss, fevers, night sweats, chills, aches and pains. Others are specific to individual body parts, such as skin rashes, coughing, or a runny nose.

In certain cases, infectious diseases may be asymptomatic for much or even all of

their course in a given host. In the latter case, the disease may only be defined as a

"disease" (which by definition means an illness) in hosts who secondarily become

ill after contact with an asymptomatic carrier. An infection is not synonymous with

an infectious disease, as some infections do not cause illness in a host.[5]

Bacterial and viral infections can both cause the same kinds of symptoms. It can be

difficult to distinguish which is the cause of a specific infection.[6] It's important to

distinguish, because viral infections cannot be cured by antibiotics.[7]

Comparison of viral and bacterial infection

Characteristic	Viral infection	Bacterial infection
Typical symptoms	In general, viral infections are systemic. This means they involve many different parts of the body or more than one body system at the same time; i.e. a runny nose, sinus congestion, cough, body aches etc. They can be local at times as in viral conjunctivitis or "pink eye" and herpes. Only a few viral infections are painful, like herpes. The pain of viral infections is often described as itchy or burning.[6]	The classic symptoms of a bacterial infection are localized redness, heat, swelling and pain. One of the hallmarks of a bacterial infection is local pain, pain that is in a specific part of the body. For example, if a cut occurs and is infected with bacteria, pain occurs at the site of the infection. Bacterial throat pain is often characterized by more pain on one side of the throat. An ear infection is more likely

		to be diagnosed as bacterial if the pain occurs in only one ear.[6] A cut that produces pus and milky-colored liquid is most likely infected.[8]
Cause	Pathogenic viruses	Pathogenic bacteria

Pathophysiology.

There is a general chain of events that applies to infections. For infections to occur,

a given chain of events must occur.[9] The chain of events involves several steps—

which include the infectious agent, reservoir, entering a susceptible host, exit and

transmission to new hosts. Each of the links must be present in a chronological

order for an infection to develop. Understanding these steps helps health care

workers target the infection and prevent it from occurring in the first place.[10]

Colonization.and INFECTION

Infection begins when an organism successfully colonizes by entering the

body,

growing and multiplying. Most humans are not easily infected. Those

who are

weak, sick, malnourished, have cancer or are diabetic have increased susceptibility

to chronic or persistent infections. Individuals who have a suppressed immune system are particularly susceptible to opportunistic infections. Entrance to the host at host-pathogen interface, generally occurs through the mucosa in orifices like the oral cavity, nose, eyes, genitalia, anus, or the microbe can enter through open wounds. While a few organisms can grow at the initial site of entry, many migrate and cause systemic infection in different organs. Some pathogens grow within the host cells (intracellular) whereas others grow freely in bodily fluids. Wound colonization refers to non replicating microorganisms within the wound, while in infected wounds, replicating organisms exist and tissue is injured. All multicellular organisms are colonized to some degree by extrinsic organisms, and the vast majority of these exist in either a mutualistic or commensal relationship with the host. An example of the former is the anaerobic bacteria species, which colonizes the mammalian colon, and an example of the latter is various species of staphylococcus that exist on human skin. Neither of these colonizations are considered infections. The difference between an infection and a colonization is often only a matter of circumstance. Non-pathogenic organisms can become pathogenic given specific conditions, and even the most virulent organism requires certain circumstances to cause a compromising infection. Some colonizing bacteria, such as *Corynebacteria sp.* and *viridans streptococci*, prevent the adhesion and

colonization of pathogenic bacteria and thus have a symbiotic relationship with the host, preventing infection and speeding wound healing.

The variables involved in the outcome of a host becoming inoculated by a pathogen and the ultimate outcome include:

- the route of entry of the pathogen and the access to host regions that it gains
- the intrinsic virulence of the particular organism
- the quantity or load of the initial inoculant
- the immune status of the host being colonized

As an example, the staphylococcus species remains harmless on the skin, but, when present in a normally sterile space, such as in the capsule of a joint or the peritoneum, multiplies without resistance and creates a burden on the host.

It can be difficult to know which chronic wounds are infected. Despite the huge number of wounds seen in clinical practice, there are limited quality data for evaluated symptoms and signs..

Disease

Disease can arise if the host's protective immune mechanisms are compromised and the organism inflicts damage on the

host. Microorganisms can cause tissue damage by releasing a variety of toxins or destructive enzymes. For example, Clostridium tetani releases a toxin that paralyzes muscles, and staphylococcus releases toxins that produce shock and sepsis. Not all infectious agents cause disease in all hosts. For example less than 5% of individuals infected with polio develop disease[]. On the other hand, some infectious agents are highly virulent. The prion that which causing mad cow disease

Persistent infections occur because the body is unable to clear the organism after the initial infection. Persistent infections are characterized by the continual presence of the infectious organism, often as latent infection with occasional recurrent relapses of active infection. There are some viruses that can maintain a persistent infection by infecting different cells of the body. Some viruses once acquired never leave the body. A typical example is the herpes virus, which tends to hide in nerves and become reactivated when specific circumstances arise.

Persistent infections cause millions of deaths globally each year.[12] Chronic infections by parasites account for a high morbidity and mortality in many underdeveloped countries.

The Infectious Disease Spectrum

By now, you probably appreciate the complexity of the factors that work together to cause the transmission of infectious agents. The *impact* of disease agents on human host populations is also a bit complex. If a large number of individuals are equally exposed to an infectious agent, they do not all respond in the same manner. In fact, there may be a broad range of responses:

- Some do not become infected at all
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Part of this variation is due to the capacity of the agent to produce disease. Infection of a healthy adult population with salmonella is likely to result in mostly inapparent or mild cases, with only a few people with more severe symptoms and very few deaths. On the other end of the spectrum, infections with rabies almost always result in severe illness and death.

Part of the variation is due to differing levels of resistance of the hosts. If measles is introduced into a highly immunized population, then most individuals do not become infected. If measles is introduced into an unimmunized, nutritionally deprived population, the spectrum shifts toward severe symptoms and a high death rate.

The existence of the infectious disease spectrum can make it challenging to find out the extent of transmission in a particular population. Most cases with inapparent or mild symptoms will never be discovered or reported, since these people will not seek health care. So when moderate or severe cases are reported, they may represent the "tip of the iceberg."

Another challenge is posed by the fact that many diseases look alike. A variety of agents may produce essentially similar clinical syndromes. For example, the signs and symptoms of tuberculosis, other mycobacteria, and histoplasmosis may be the same. However, effective treatment and control measures are very different for these three diseases. This is why laboratory identification of the specific disease agent is so important in any epidemiological investigation.

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Dr.Rasmiya Abd Aburesha

Lect 2

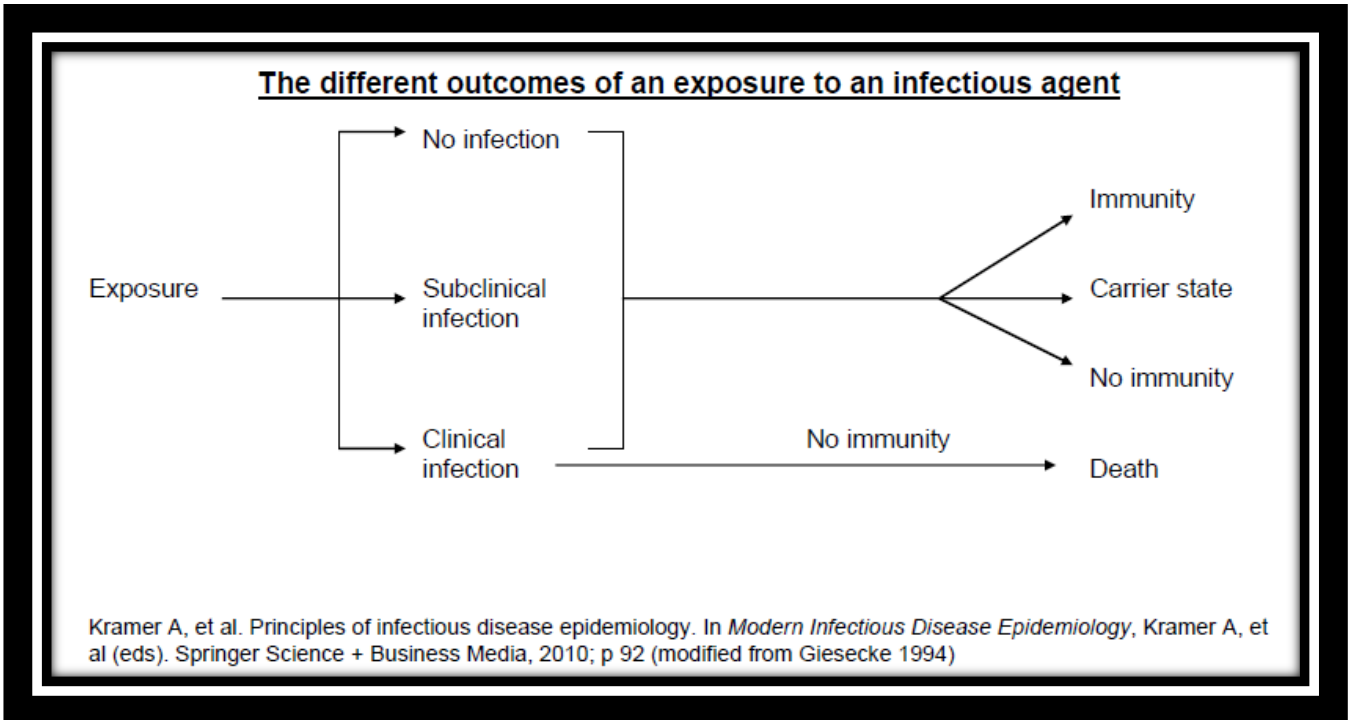
Microbiological Classification of Infectious Diseases

Disease is a disturbance in the state of health

• Microbes cause disease in the course of stealing space, nutrients, and/or living tissue from their symbiotic hosts (e.g., us)

• To do this, microbes do most of the following:

– Gain access to the host (contamination)
– Adhere to the host (adherence)
– ReReplicate on the host (colonization)
– Invade tissues other agents that cause host harm (invasion)
– Produce toxins or other agents that cause host harm (damage)



BIOLOGIC CHARACTERISTICS OF INFECTIOUS AGENTS:

Infectivity – the ability to infect a host
• ***Pathogenicity*** – the ability to cause disease in the host
• ***Virulence*** – the ability to cause severe disease in the host
• ***Immmunogenicity*** –the ability to induce an immune reresponse in the hosts.

Infectious Disease Terms

Infectious dose – number of organisms needed to successfully infect

Incubation period – interval from exposure to clinical symptoms

Infectious period – interval during which host can transmit infection

Reproductive rate – ability of an agent to spread

Outbreak – limited spread

Endemic – usually present; steady prevalence

Epidemic – rapid spread

Pandemic — occurring across countries and in multiple populations

Table 19.1 Terms Used in the Study of Infectious Diseases

Term	Definition
Bacteremia	Bacteria circulating in the bloodstream
Colonization	Establishment and growth of a microorganism on a body surface
Disease	Noticeable impairment of body function
Immunocompromised	A host with weaknesses or defects in the innate or adaptive defenses
Inapparent infection	Infection with no obvious symptoms
Infectious disease	Disease caused by an infecting microorganism or virus
Latent infection	Infection in which the infectious agent is present but not active
Opportunistic pathogens	Organisms that cause disease only when introduced into an unusual location or into an immunocompromised host
Parasite	An organism that benefits at the expense of another organism, the host
Pathogen	Any disease-causing microorganism or virus
Pathogenic	Disease-causing
Primary infection	Infection in a previously healthy person
Secondary infection	An additional infection that occurs as a result of a primary infection and that occurs during or immediately following the primary infection
Septicemia	Acute illness caused by infectious agents or their products circulating in the bloodstream
Systemic infection	Widespread infection through blood or lymph
Toxemia	Toxin circulating in the bloodstream
Viremia	Viruses circulating in the bloodstream
Virulence determinants	Attributes of a microorganism or virus that promote pathogenicity

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MODES OF TRANSMISSION

- Direct
  - – Droplet
  - – Aerosol
  - – Skin to skin
- Indirect
  - – Fomites (clothes, blankets, door handles etc)
  - – Vectors (e.g. mosquitoes)
  - – Food and water

– Intermediate hosts

Measures of Disease Occurrence

Measure	Description
Prevalence	Number or proportion of persons with a specific disease at a specific time point in the population
Incidence	Number or proportion of persons developing a specific disease during a time period
Morbidity	Ambiguously used: prevalence or incidence
Mortality	Number or proportion of persons dying during a time period
Fatality rate	Proportion of persons dying from a specific disease among all persons with the disease
Attack rate	Proportion of cases developing the disease among all persons who were exposed to the disease

Mikolajczyk R. Methods and concepts of epidemiology. In *Modern Infectious Disease Epidemiology*, Kramer A, et al (eds). Springer Science + Business Media, 2010; p 193

Acute and chronic disease

Many individuals confuse the difference between an acute disease and a chronic disease. An acute disease lasts for just a short time but can begin rapidly and have intense symptoms. By contrast, a chronic disease produces symptoms that last for three months or more.

Acute

Often, people are confused about what constitutes an acute disease. They believe that an acute disease is always severe. In reality, an acute disease can be mild, severe or even fatal. The term "acute" does not indicate the severity of the disease. Instead, it indicates how long the disease lasts and how quickly it develops. Examples of acute diseases include colds, influenza and strep throat.

Subacute

Diseases that fall between what normally are considered acute diseases and chronic diseases are sometimes referred to as subacute diseases. A disease might be considered acute at first, then subacute after a few days or a few weeks. If the disease continues for several months, it might then be called a chronic disease. There are no standard time periods that are used to determine whether a disease is acute, subacute or chronic, so their precise definitions can vary, depending on who is making the determination.

Chronic

A chronic disease is persistent. It lasts for a long period of time and might recur. Like an acute disease, a chronic disease can be mild, severe or fatal. Examples of chronic diseases include cancer, heart disease, kidney disease

and diabetes. Unlike an acute disease, a chronic disease is likely to develop over time instead of having a sudden onset.

latent infection

is a situation in which a virus is present in the body, but it remains dormant, not causing any overt symptoms. The patient is still infected with the virus, and he or she can pass the virus on to others when they are exposed to the dormant virus. Latent infections can also be activated, causing symptoms and illness to emerge again. A classic example of a latent infection is herpes simplex, which periodically flares up to cause cold sores before going dormant again.

People sometimes confuse latent infections with latency. Latency or clinical latency is one of the things which occurs during the incubation period of an infection, in which the causative agent is present in the body and multiplying, but not causing symptoms. The virus involved in clinical latency is not dormant, as is the case with latent infections, but fully active and causing problems for the host organism. Eventually, the virus will move out of latency and start causing detectable symptoms, alerting the host to the fact that an infection is occurring.

Some infections can never be fully flushed from the body, becoming latent with the use of medications and other measures to control the virus and

inhibit replication. In these cases, the latent infection may periodically flare up in response to environmental cues. Latent infections can also be caused when a virus mutates, becoming impossible to eradicate, or when a course of treatment is not completed, allowing a virus to remain dormant in the body.

A number of viruses are characterized by causing latent infection, allowing the virus to ebb and flow in the body in cycles as the environment changes. From the point of view of the virus, the ability to go dormant is critical, as it allows the virus to retain a host while becoming dormant when conditions are hostile or unpleasant for the virus. Latent infections can also be very hard to detect, or to manage.

THE CHAIN and progression OF INFECTION

In order for infection and disease to occur in an individual, a process involving six related components must occur. This process has been referred to as the “Chain of Infection.” The six steps or “links” in the chain are:

- Etiologic agent
- Reservoir
- Portal of Exit

• Mode of Transmission

• Portal of Entry

• Susceptible Host

In this module, we will examine each of these links and some other important concepts that help us understand infectious disease transmission. To stop the spread of disease, one or more of these links must be broken.

A. Etiologic Agents

There are seven categories of biological agents that can cause infectious diseases. Each has its own particular characteristics. The types of agents are:

1. Metazoa
2. Protozoa
3. Fungi
4. Bacteria
5. Rickettsia
6. Viruses
7. Prions

1. **Metazoa** are multicellular animals, many of which are parasites. Among the diseases they cause are:

a. Trichinellosis, also called trichinosis, caused by an intestinal roundworm transmitted through undercooked meat.

b. Hookworm, transmitted through feces-contaminated water and soil. Infestation can cause chronic anemia that often results in retarded mental and physical development of children.

c. Schistosomiasis, caused by a blood fluke and transmitted through contaminated water. Symptoms are related to the number and location of eggs in the human body, and may involve the liver, intestines, spleen, urinary tract, and reproductive system.

2. **Protozoa** are single-cell organisms with a well-defined nucleus. Some of these are human parasites. Examples of diseases cause by protozoa include:

a. Malaria, a mosquito-borne disease that is one of the top three infectious diseases in the world (along with tuberculosis and HIV).

b. Giardiasis, an infection of the upper small intestine that causes a diarrheal illness. Outbreaks can be difficult to control, especially in child care settings

c. Toxoplasmosis, transmitted to humans from cats and undercooked meat. When this systemic disease infects a pregnant woman, it can cause the death of the fetus.

d. Pneumocystis carinii pneumonia or PCP, which is often fatal, especially in people with compromised immune systems such as those infected with HIV.

3. **Fungi** are nonmotile, filamentous organisms that cause diseases that can be very difficult to treat. Some examples important to public health are:

a. Histoplasmosis, transmitted by inhaling dust from soil that contains bird droppings. The severity varies widely, with the lungs the most common site of infection.

b. Candidiasis, transmitted by contact with human patients and carriers. This fungus causes lesions on the skin or mucous membranes, including “thrush” and vulvovaginitis. Symptoms can be severe in immunocompromised people.

4. **Bacteria** are single-celled organisms that lack a nucleus. They are responsible for a wide range of human diseases, including:

a. Tuberculosis, a chronic lung disease that is a major cause of disability and death in many parts of the world.

b. Staphylococcal disease, which can affect almost every organ system. Severity ranges from a single pustule of impetigo, through pneumonia, arthritis, endocarditis, etc., to sepsis and death.

c. Chlamydia and gonorrhea, the most widespread sexually transmitted diseases.

d. Tetanus and diphtheria, two diseases that were once major public health problems but are now well controlled through immunization.

d. Other vaccine-preventable diseases caused by bacteria are:

- Pertussis
- Haemophilus influenzae type b (Hib)
- Pneumococcal disease.

5. **Rickettsia** are a genus of bacteria usually found in the cells of lice, ticks, fleas and mites. They are smaller than most bacteria and share some characteristics of viruses. Diseases cause by rickettsia include:

a. Rocky Mountain Spotted Fever, a tick-borne systemic disease that can be hard to diagnose and that leads to death in 3-5% of US cases.

b. Typhus, a louse-borne rash illness with a high case-fatality rate that has occurred historically in poor living conditions brought on by war and famine.

6. **Viruses** are very small, consisting of an RNA or DNA core and an outer coat of protein. They can reproduce and grow only inside of living cells. Many viral illnesses are significant to public health, including:

a. Influenza, a respiratory illness that contributes to development of pneumonia and occurs in annual epidemics during the winter months

b. HIV (human immunodeficiency virus), that causes Acquired Immunodeficiency Syndrome (AIDS). This severe, life-threatening pandemic disease has spread worldwide within the past 20-30 years.

c. Rabies, that is spread to humans from animal bites or scratches. Rabies is almost always fatal in humans but is preventable by a vaccine.

d. Measles, mumps, rubella, and poliomyelitis are all well controlled in the US through immunization.

7. **Prions** are infectious agents that do not have any genes. They seem to consist of a protein with an aberrant structure, which somehow replicates in animal or human tissue. Prions cause severe damage to the brain.

B. Reservoirs

The next essential link in the chain of infection is the reservoir, the usual habitat in which the agent lives and multiplies. Depending upon the agent, the reservoir may be:

- humans,
- animals,
- environment

When working with any disease agent, it is important to learn about its usual reservoir(s).

1. **Human Reservoirs**

There are two types of human reservoirs, acute clinical cases and carriers.

a. Acute clinical cases are people who are infected with the disease agent and become ill.

- Because they are ill, their contacts and activities may be limited.

- They are also more likely to be diagnosed and treated than carriers are.

b. Carriers, on the other hand, are people who harbor infectious agents but are not ill.

- Carriers may present more risk for disease transmission than acute clinical cases, because their contacts are unaware of their infection, and their activities are not restricted by illness.
- Depending on the disease, any of the following types of carriers may be important:
  - Incubatory carriers
  - Inapparent infections (also called subclinical cases)
  - Convalescent carriers
  - Chronic carriers

Incubatory carriers are people who are going to become ill, but begin transmitting their infection before their symptoms start. Examples:

measles: a person infected with measles begins to shed the virus in nasal and throat secretions a day or two before any cold symptoms or rash are noticeable. Many other diseases also have an incubatory carrier phase. Most notably, HIV infection may be present for years before the person develops any symptoms.

Inapparent infections: People with inapparent infections never develop an illness, but are able to transmit their infection to others. With some diseases, inapparent infections are more common than acute clinical cases. Example: Of every 100 individuals infected with the poliomyelitis virus, only one becomes paralyzed. Four

others will have a mild illness with fever, malaise, headache, nausea and vomiting. But 95 out of the 100 will have no symptoms at all, although they pass the virus in their feces.

Sometimes the likelihood of an inapparent infection depends on another epidemiologic factor, such as age. Hepatitis A is a good example of this. Over 50% of adults infected with this virus develop symptoms. However, among children under 5, there may be 10 inapparent infections for every child who develops jaundice. So children are very effective spreaders of the hepatitis A virus, which is passed in the feces regardless of the presence of symptoms.

Subclinical infections: With some diseases, such as meningococcal meningitis, the number of subclinical cases may be quite high before a single clinical case appears. On some military bases where outbreaks have occurred, the carrier rate has been documented at 50% or more.

Convalescent carriers are people who continue to be infectious during and even after their recovery from illness. This happens with many diseases. Example: Salmonella patients may excrete the bacteria in feces for several weeks, and rarely even for a year or more. This is most common in infants and young children. Treatment with inappropriate antibiotics may prolong the convalescent carrier phase.

Chronic carriers are people who continue to harbor infections for a year or longer after their recovery. Example: the chronic carrier state is not uncommon following hepatitis B infection, whether or not the person became ill, and may be lifelong. The risk of developing chronic hepatitis B depends on the person's age at infection. About 90% of infants infected at birth become chronic carriers of the disease, compared with only 1-10% infected after age 5. That is why it is so important to give hepatitis B vaccine to newborns.

2. **Animal Reservoirs**

Animal reservoirs of infectious agents can be described in the same way as human reservoirs. They may be

- acute clinical cases, or
- carriers.

Depending upon the disease, different carrier phases may be important in transmission.

3. **Environmental Reservoirs**

Plants, soil and water may serve as the reservoir of infection for a variety of diseases.

- Most fungal agents (mycoses) live and multiply in the soil.

Examples:

- The organism that causes histoplasmosis lives in soil with high organic content and undisturbed bird droppings.
- The agents that cause tetanus, anthrax and botulism are widely distributed in soil.
- The agent of Legionnaire's Disease lives in water, including hot water heaters.

C. Portal of Exit

The next link in the chain of disease transmission is the portal of exit, **the route by which the disease agent may escape from the human or animal reservoir**. While many disease agents have only one portal of exit, others may leave by various portals.

The portals most commonly associated with human and animal diseases are:

- Respiratory
- Genitourinary

• Alimentary

• Skin

Superficial lesions Percutaneous

• Transplacental

1. **Respiratory**: This is the route of many disease agents that cause respiratory illnesses such as the common cold, influenza, and tuberculosis. It is also the route used by many childhood vaccine-preventable diseases, including measles, mumps, rubella, pertussis, *Haemophilus influenzae* type b (Hib), and pneumococcal disease. This is the ***most important portal and the most difficult to control***.

2. **Genitourinary**: This portal of exit is the route of sexually transmitted diseases, including syphilis, gonorrhea, chlamydia, and HIV. Schistosomiasis, a parasitic disease, and leptospirosis, a bacterial infection, are both spread through urine released into the environment.

3. **Alimentary**: The alimentary portal of exit may be the mouth, as in rabies and other diseases transmitted by bites. More commonly, disease agents are spread by the other end of the intestinal tract. These are referred to as enteric diseases. In general, enteric diseases may be

controlled through good hygiene, proper food preparation and sanitary sewage disposal. Examples include:

- *Hepatitis A*
- *Salmonella,* including *typhoid*
- *Shigella* • *Cholera* • *Giardia* • *Campylobacter*

4. **Skin**: Skin may serve as a portal of exit through superficial lesions or through percutaneous penetration.

- Superficial skin lesions that produce infectious discharges are found in smallpox, varicella (chickenpox), syphilis, chancroid, and impetigo.
- Percutaneous exit occurs through mosquito bites (malaria, West Nile virus) or through the use of needles (hepatitis B and C, HIV).

5. **Transplacental**: This portal of exit from mother to fetus is important in the transmission of rubella, HIV, syphilis, and cytomegalovirus (the most

common infectious cause of developmental disabilities). It is, fortunately, not a factor for most diseases.

D .Transmission and mode of transmission

A mode of transmission is necessary to bridge the gap between the portal of exit from the reservoir and the portal of entry into the host. The two basic modes are **direct** and **indirect**.

1. **Direct transmission** occurs more or less immediately. Many diseases are transmitted by direct contact with the human, animal or environmental reservoir. Prime

examples are sexually transmitted diseases and enteric diseases such as shigella, giardia and campylobacter. Contact with soil may lead to mycotic (fungal) diseases.

Droplet spread is also considered direct transmission. Infectious aerosols produced by coughing or sneezing can transmit infection directly to susceptible people up to three feet away. Many respiratory diseases are spread this way.

2. **Indirect transmission** may occur through animate or inanimate mechanisms.

• *Animate mechanisms* involve vectors. Flies may transmit infectious agents such as shigella in a purely mechanical way, by walking on feces and then on food. Mosquitoes, ticks or fleas may serve as reservoirs for the growth and multiplication of agents, for example in malaria or Lyme disease.

• *Inanimate mechanisms*: When disease agents are spread by environmental vehicles or by air, this is referred to as indirect transmission by *inanimate mechanisms*. Anything may be a vehicle, including objects, food, water, milk, or biological products.

- Food is a common vehicle for salmonella infections
- Water is the usual vehicle in cholera outbreaks
- Surgical instruments and implanted medical devices may be the vehicles of staphylococcal infections

Indirect, airborne transmission is important in some respiratory diseases. This occurs when very tiny particles of respiratory material become suspended in the air (called aerosols). Such particles may remain suspended and stay infectious for varying periods of time. They are particularly dangerous because their size (1 to 5 microns) allows them to be drawn deep into the lungs and retained. Tuberculosis is spread this way, as is measles in certain settings such as doctors' offices. Air may also spread particles of various sizes from contaminated soil, or from objects such as clothing and floors.

E. Portals of Entry

The portal of entry into the host is usually the same as the portal of exit from the reservoir.

In some diseases, however, the exit and entry portals may differ. Example: staphylococcal bacteria may escape from one person's respiratory tract to infect another person's skin lesion. If that person is a foodhandler, the staphylococcal bacteria may escape from the infected skin lesion, contaminate food where it can incubate, and cause "food poisoning" in people eating the food

F..Susceptible Host :

The last essential component in the chain of infection is the susceptible host. Susceptibility is affected by:

- Genetic factors
- General resistance factors
- Specific acquired immunity

1. **Genetic factors** The role of *genetic factors* in susceptibility to infectious diseases is not yet well understood. Genes do seem to play a role in the progression of HIV disease, and perhaps in individuals' susceptibility to meningococcal meningitis.

2. **General resistance factors** include many body functions that we take for granted. Intact skin and mucous membranes help us resist disease. So do the gastric acid in our stomachs, the cilia in our respiratory tracts, and the cough reflex.

3. **Specific acquired immunity** is the greatest influence on host susceptibility. This immunity is specific to a particular disease agent, and it may be acquired naturally or artificially.

- Natural immunity may be acquired by experiencing an infection, which is called "active natural immunity." Many diseases confer immunity after a single infection, but many others do not. A single bout of measles or chickenpox, for example, confers lifelong immunity to that disease. Influenza and salmonella are examples of infections that do not confer immunity and therefore may recur.

Another mechanism of natural immunity is the transfer of antibodies from the mother to the newborn child, via the placenta and/or breast milk. This is called "passive natural immunity," and it diminishes after varying lengths of time. It is very important in giving infants a good head start in life.

- Artificial immunity may be acquired through the use of vaccines, toxoids and immune globulins.

 Active immunity: Receiving a vaccine or toxoid stimulates "active" immunity, since the recipient responds by producing his/her own antibodies.
 Passive immunity: Receiving an antitoxin or immune globulin confers "passive" immunity, essentially by borrowing the antibodies of other people. Passive immunity lasts for only a short time, while active immunity usually lasts much longer, even for a lifetime.

Lect 4 Communicable and non communicable:

Communicable diseases are contagious illnesses that can be transmitted between people or animals in a variety of ways. All communicable diseases are transmitted via some form of infectious pathogen, such as bacteria or viruses. The World Health Organization (WHO) estimates that over 16 million deaths occur world-wide each year from communicable diseases.

Communicable diseases are the diseases that are caused by infectious agents and can be transmitted from an infected person to other people, animals, or other sources in the environment.

- Communicable diseases are also called infectious diseases or transmissible diseases.
- These diseases are transmitted when the infectious agents are transmitted through contact with contaminated surfaces, bodily fluids, blood products, insect bites, or through the air.
- The spread of infectious diseases might either be direct or indirect.
- In the direct transmission, the infectious agent is transferred through close physical contact, whereas in

indirect transmission, the agent is transferred through air, water, or other vectors.

- After these agents enter the body of a healthy individual, the organism undergoes a period of time called the incubation period. Once this period is over, the symptoms of the disease begin to appear.
- In most cases, the immune system of the body tends to destroy infectious agents. However, the disease appears when the organism escapes the immune system.
- Communicable diseases might be seasonal where certain diseases occur at a certain time of the year. One example of this is malaria, which occurs mostly during the breeding season of the female mosquito.
- The symptoms of communicable diseases might differ with the nature of the disease; however, the common symptoms are fever, diarrhea, headache, muscle ache, fatigue, etc.
- Most communicable diseases are acute diseases where the disease and symptoms appear over a short time.
- Communicable diseases, however, are not considered severe as the treatment for these diseases are available.

Types

- A number of different types of pathogens cause communicable diseases in humans. Bacteria are responsible for some of the most prevalent communicable diseases, including tuberculosis, pneumonia, diphtheria and streptococcus infections. Pathogenic viruses also

transmit contagious illnesses such as the common cold, the flu, HIV, hepatitis, measles and mumps. Other agents that cause infectious diseases include fungi and parasites.

- Communicable diseases can be spread in a number of ways. Pathogens can be transmitted via the air, direct touch, infected objects, sexual contact or infected food and water. Fleas, rats, mosquitoes, ticks and mice are also common carriers of communicable diseases. Knowing the mode of transmission for a communicable disease is vital in the treatment and management of an illness.

Identification

- Diagnosis of communicable diseases involves a wide range of medical tools. Some illnesses, such as the common cold, can be diagnosed by clinical symptoms alone. Frequently infectious diseases are confirmed with diagnostic tests engineered to detect a specific virus or bacteria such as HIV and hepatitis. Additional methods of communicable disease identification include bacterial cultures,

microscopic examination and a variety of general laboratory tests.

Effects

- The effects communicable diseases have on the human body are as varied as the diseases themselves. Many communicable diseases create some discomfort for a period of time but have no lasting long-term effects. There are, however, many contagious illnesses that can generate long-term disability or death, such as HIV, malaria, pneumonia, tuberculosis and ebola.

Non-communicable disease:

Non-communicable diseases definition

Non-communicable diseases are the diseases that are not transferred from an infected person to another via any means and are mostly caused by factors like improper lifestyle and eating habits.

- Non-communicable diseases are also called non-contagious or non-infectious diseases.
- Infectious agents like bacteria and viruses do not cause these diseases, and thus these diseases do not

spread from an infected person to a healthy individual.

- Most non-communicable diseases are caused due to an unhealthy diet and lifestyle. However, other causes like mutations, heredity and environmental changes might also trigger some non-communicable diseases.
- Non-communicable diseases, unlike communicable diseases, are not seasonal and might occur at any time of the year.
- Diseases like cancer and diabetes might even be hereditary, which are inherited from parents to the offsprings.
- These diseases are also more chronic as the symptoms appear gradually and thus are difficult to diagnose. Most of the non-communicable diseases pose severe and long-lasting health effects on the patients.
- Some chronic non-communicable diseases might even have periods of temporary relapse where the disease disappears for a short period of time regularly only to reappear again.
- Non-communicable diseases are also found to be more severe, responsible for about 70% of all deaths worldwide.
- There are no specific treatments available for most non-communicable diseases, and the available medicines simply prevent the disease from getting worse. Most non-communicable diseases are not curable.
- However, maintaining a proper and healthy eating habit and lifestyle with regular check-ups are essential preventive measures against non-communicable diseases.

A **non-communicable diseases** NCDs may be chronic diseases of long duration and slow progression, or they may result in more rapid death such as some types of sudden stroke. They include autoimmune diseases, heart disease,stroke, many cancers, asthma, diabetes, chronic kidney disease, osteoporosis, Alzheimer's disease, cataracts, and more. While sometimes (incorrectly) referred to as synonymous with "chronic diseases", NCDs are distinguished only by their non-infectious cause, not necessarily by their duration. Some chronic diseases of long duration, such as HIV/AIDS, are caused by transmittable infections. Chronic diseases require chronic care management as do all diseases that are slow to develop and of long duration.

The World Health Organization (WHO) reports NCDs to be by far the leading cause of death in the world, representing over 60% of all deaths. Out of the 36 million people who died from NCDs in 2005, half were under age 70 and half were women.[1] Of the 57 million global deaths in 2008, 36 million were due to NCDs.[2] That is approximately 63% of total deaths

worldwide. Risk factors such as a person's background, lifestyle and environment are known to increase the likelihood of certain NCDs. Every year, at least 5 million people die because of tobacco use and about 2.8 million die from being overweight. High cholesterol accounts for roughly 2.6 million deaths and 7.5 million die because of high blood pressure.

Causes and risk factors

Risk factors such as a person's background; lifestyle and environment are known to increase the likelihood of certain non-communicable diseases. They include age, gender,genetics, exposure to air pollution, and behaviours such as smoking, unhealthy diet and physical inactivity which can lead to hypertension and obesity, in turn leading to increased risk of many NCDs.Most NCDs are considered preventable because they are caused by modifiable risk factors.

The WHO's *World Health Report 2002* identified five important risk factors for non-communicable disease in the top ten leading risks to health. These are raised blood pressure, raised cholesterol, tobacco use, alcohol consumption, and overweight.The other factors associated with higher risk of NCDs include a person's economic and social conditions, also known as the "[social determinants of health]."

It has been estimated that if the primary risk factors were eliminated, 80% of the cases of heart disease, stroke and type 2 diabetes and 40% of cancers could be prevented. Interventions targeting the main risk factors could have a significant impact on reducing the burden of disease worldwide. Efforts focused on better diet and increased physical activity have been shown to control the prevalence of NCDs

Environmental diseases

NCDs include many [environmental disease], covering a broad category of avoidable and unavoidable human health conditions caused by external factors, such as sunlight, nutrition, pollution, and lifestyle choices.
The diseases of affluence are non-infectious diseases with environmental causes. Examples include:

- Many types of cardiovascular disease (CVD)
- Chronic obstructive pulmonary disease (COPD) caused by smoking tobacco
- Diabetes mellitus type 2
- Lower back pain caused by too little exercise
- Malnutrition caused by too little food, or eating the wrong kinds of food (e.g. scurvy from lack of Vitamin C)
- Skin cancer caused by radiation from the sun

Inherited diseases

Genetic disorders are caused by errors in genetic information that produce diseases in the affected people. The origin of these genetic errors can be:

- Spontaneous errors or mutations to the genome:
    - A change in chromosome numbers, such as Down syndrome.
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  Cystic fibrosis is an example of an inherited disease that is caused by a mutation on a gene. The faulty gene impairs the normal movement of sodium chloride in and out of cells, which causes the mucus-secreting organs to produce abnormally thick mucus. The gene is recessive, meaning that a person must have two copies of the faulty gene for them to develop the disease. Cystic fibrosis affects the respiratory, digestive and reproductive systems, as well as the sweat glands. The mucus secreted is very thick and blocks passageways in the lungs and digestive tracts. This mucus causes problems with breathing and with the digestion and absorption of nutrients.

- Inherited genetic errors from parents:

- Dominant genetic diseases, such as Huntingtons, require the inheritance of one erroneous gene to be expressed.

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Communicable vs non Communicable

Basis for Comparison	Communicable diseases	Non-communicable diseases
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Also called	Communicable diseases are also known as infectious diseases.	Non-communicable diseases are also known as chronic diseases.
Progression	These are more likely to be acute, meaning they appear quickly.	These are more likely to be chronic, meaning they last for a longer period of time and progress gradually.
Seasonal	Some infectious diseases might be seasonal.	Non-communicable diseases are not seasonal and might occur at any time of the year.

Cause	Pathogenic microorganisms are the primary cause of communicable diseases.	These are caused by nutrition deficiency, hormonal deficiency, or abnormal proliferation of cells.
Inherited	Communicable diseases cannot be inherited from one generation to another.	Non-communicable diseases might be inherited from one generation to another.
Agents/Vectors	Viruses, fungi, and bacteria act as agents/vectors for infection and transmission of such diseases.	There are no agents for infection of non-communicable diseases as they primarily depend on the personal diet, allergy, or physical inactivity.
Spread	There are many reasons for the spread of communicable diseases. It can spread through the air, by direct contact with a contaminated surface, food, etc.	These do not spread from one person to another at all.
Organs affected	The most common communicable diseases are those of respiratory tracts, such as common cold, influenza, tuberculosis.	Non-communicable diseases are varied, such as cardiovascular disease, diabetes, etc.
Symptoms	Symptoms of communicable diseases can be observed as quickly as a day or two from the entry of the pathogen.	Symptoms for non-communicable diseases may not be observed until a year or more, which increases the risk of the disease being fatal.

Severity	These are less severe, i.e. they develop quickly and pose a short-term threat to the patient.	These are more severe, responsible for more deaths worldwide. These diseases also have long-term effects on the life of the patient.
Relapse	There are no periods for relapse for infectious diseases.	There might be multiple periods of relapse during the diseases.
Diagnosis	For many communicable diseases, accurate diagnostic tests are available.	Accurate diagnostic tests are not available for most non-communicable diseases.
Treatment	These can be treated with a short treatment schedule.	These require prolonged treatment.
Curability	Almost all communicable diseases can be cured except for HIV/AIDS.	Non-communicable diseases such as cancer and diabetes do not have any specific cure.
Prevention	These can be prevented by some conventional methods such as maintaining personal hygiene, avoid sharing eating utensils, etc.	These need special surgical operations for treatment.
Examples	Diseases like typhoid, cholera, malaria, tuberculosis, leprosy are examples of communicable diseases.	Diseases like cancer, diabetes, Alzheimer's diseases, Down's syndrome, Kwashiorker are examples of non-communicable diseases.

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Inherited	Communicable diseases cannot be inherited from one generation to another.	Non-communicable diseases might be inherited from one generation to another.
Agents/Vectors	Viruses, fungi, and bacteria act as agents/vectors for infection and transmission of such diseases.	There are no agents for infection of non-communicable diseases as they primarily depend on the personal diet, allergy, or physical inactivity.
Spread	There are many reasons for the spread of communicable diseases. It can spread through the air, by direct contact with a contaminated surface, food, etc.	These do not spread from one person to another at all.
Organs affected	The most common communicable diseases are those of respiratory tracts, such as common cold, influenza, tuberculosis.	Non-communicable diseases are varied, such as cardiovascular disease, diabetes, etc.
Symptoms	Symptoms of communicable diseases can be observed as quickly as a day or two from the entry of the pathogen.	Symptoms for non-communicable diseases may not be observed until a year or more, which increases the risk of the disease being fatal.

Severity	These are less severe, i.e. they develop quickly and pose a short-term threat to the patient.	These are more severe, responsible for more deaths worldwide. These diseases also have long-term effects on the life of the patient.
Relapse	There are no periods for relapse for infectious diseases.	There might be multiple periods of relapse during the diseases.
Diagnosis	For many communicable diseases, accurate diagnostic tests are available.	Accurate diagnostic tests are not available for most non-communicable diseases.
Treatment	These can be treated with a short treatment schedule.	These require prolonged treatment.
Curability	Almost all communicable diseases can be cured except for HIV/AIDS.	Non-communicable diseases such as cancer and diabetes do not have any specific cure.
Prevention	These can be prevented by some conventional methods such as maintaining personal hygiene, avoid sharing eating utensils, etc.	These need special surgical operations for treatment.
Examples	Diseases like typhoid, cholera, malaria, tuberculosis, leprosy are examples of communicable diseases.	Diseases like cancer, diabetes, Alzheimer's diseases, Down's syndrome, Kwashiorker are examples of non-communicable diseases.

Lect 6

Bacterial Defense against I

Some pathogenic bacteria are inherently ab

bactericidal components of host tissues, usuall

of some structural property. For example, the poly-D-glut of *Bacillus anthracis* protects the organisms against acti proteins (defensins) in sera or in phagocytes. The outer Gram-negative bacteria is a permeability barrier to lysozy easily penetrated by hydrophobic compounds such as bile tract that are harmful to the bacteria. Pathogenic mycob waxy cell wall that resists attack or digestion by most tissu And intact lipopolysaccharides (LPS) of Gram-negative p protect the cells from complement-mediated lysis or

Most successful pathogens, however, possess additiona biochemical features that allow them to resist the host c against them, i.e., the phagocytic and immune responses. breaches the host's surface defenses, it must then overc phagocytic response to succeed

Ability of Pathogens to Avoid or Overcome

Microorganisms invading tissues are first and foremos phagocytes. Bacteria that readily attract phagocytes and ingested and killed are generally unsuccessful as pathoger most bacteria that are successful as pathogens interfere t with the activities of phagocytes or in some way avoid

Bacterial pathogens have devised numerous and diverse strategies
avoid phagocytic engulfment and killing. Most are aimed at blocking o
or more of the steps in phagocytosis, thereby halting the process. Th
process of phagocytosis is discussed in the chapter on Inna
Immunity against bacterial pathogen

Avoiding Contact with Phagocyt

Bacteria can avoid the attention of phagocytes in a number of way

1. Pathogens may invade or **remain confined in regions inaccessib
to phagocytes**. Certain internal tissues (e.g. the lumens of glands, th
urinary bladder) and surface tissues (e.g. unbroken skin) are not patrolle
by phagocyte

2. Some pathogens are able to **avoid provoking an overwhelmi
inflammatory response**. Without inflammation the host is unable
focus the phagocytic defense

3. Some bacteria or their products **inhibit phagocyte chemotaxis**. F
example, Streptococcal streptolysin (which also kills phagocyte
suppresses neutrophil chemotaxis, even in very low concentration
Fractions of*Mycobacterium tuberculosis* are known to inhibit leukocy
migration. The*Clostridium ø* toxin also inhibits neutrophil chemotaxi

4. Some pathogens can cover the surface of the bacterial cell with
component which is seen as "self" by the host phagocytes and immun
system. Such a strategy **hides the antigenic surface** of the bacter
cell. Phagocytes cannot recognize bacteria upon contact and the possibili
of opsonization by antibodies to enhance phagocytosis is minimized. F
example, pathogenic *Staphylococcus aureus* produces cell-boun
coagulase and clumping factor which clots fibrin on the bacteri
surface. *Treponema pallidum*, the agent of syphilis, binds fibronectin
its surface. Group A streptococci are able to synthesize a capsu
composed of hyaluronic acid. Hyaluronic acid is the ground substan
(tissue cement) in connective tissue. Some pathogens have or can depos
sialic acid residues on their surfaces which prevents opsonization b
complement components and impedes recognition by phagocyte

Inhibition of Phagocytic Engulfme

Some bacteria employ strategies to avoid engulfment (ingestion) phagocytes do make contact with them. Many important pathoger bacteria bear on their surfaces substances that inhibit phagocyt adsorption or engulfment. Clearly it is the bacterial surface that matter Resistance to phagocytic ingestion is usually due to a component of th bacterial cell surface (cell wall, or fimbriae, or a capsule). Classic examples of antiphagocytic substances on bacterial surfaces includ

1. **Polysaccharide capsules** of *S. pneumoniae*, *Haemophil influenzae*,*Treponema pallidum* and *Klebsiella pneumonia*

2. **M protein** and **fimbriae** of Group A streptococ

3. **Surface slime** (polysaccharide) produced a **biofilm** by *Pseudomonas aeruginos*

4. **O polysaccharide** associated with LPS of *E. c*

5. **K antigen** (acidic polysaccharides) of *E. coli* or the analogous **antigen** of *Salmonella typ*

6. Cell-bound or soluble **Protein A** produced by *Staphylococcus aureu* Protein A attaches to the Fc region of IgG and blocks the cytophilic (ce binding) domain of the Ab. Thus, the ability of IgG to act as an opson factor is inhibited, and opsonin-mediated ingestion of the bacteria blocke

Survival Inside of Cell

Some bacteria survive inside of phagocytes, either neutrophils macrophages. Bacteria that can resist killing and survive or multiply insi of phagocytes or other cells are considered intracellular parasites. Th intracellular environment of a phagocyte may be a protective on protecting the bacteria during the early stages of infection or until the develop a full complement of virulence factors. The intracellul environment also guards th bacteria against the activities of extracellular bactericides, antibodie drugs, etc. Some bacteria that are intracellular parasites because the able to invade eucaryotic cells are listed in Table

Table 1. BACTERIAL INTRACELLULAR PATHOGEN

Organism	Disease
Mycobacterium tuberculosis	Tuberculosis
Mycobacterium leprae	Leprosy
Listeria monocytogenes	Listeriosis
Salmonella typhi	Typhoid Fever
Shigella dysenteriae	Bacillary dysentery
Yersinia pestis	Plague
Brucella species	Brucellosis
Legionella pneumophila	Pneumonia
Rickettsiae	Typhus; Rocky Mountain Spotted Fever
Chlamydia	Chlamydia; Trachoma

Some intracellular parasites have special genetically-encod mechanisms to get themselves into host cells that are nonphagocyti Pathogens such as*Yersinia*, *Listeria*, *E. co Salmonella*, *Shigella* and *Legionella* possess complex machinery f cellular invasion and intracellular survival. These systems involve variou types of non-toxin virulence factors. Sometimes these factors are referr to as bacterial **invasins**. Still other bacteria such as *Bordete pertussis* and *Streptococcus pyogenes,* have recently been discovered the intracellular habitat of epithelial cell

Legionella pneumophila enters mononuclear phagocytes by depositin complement C3b on its surfaces and using that host protein to serve as ligand for binding to macrophage cell surfaces. After ingestion, th bacteria remain in vacuoles that do not fuse with lysosomes, apparent due to the influence of soluble substances produced by the bacteri

Salmonella bacteria possesses an **invasin operon** (inv A - H) th encodes for factors that regulate their entry into host cells. Mutations the operon yield organisms that can adhere to target cells without bein internalized. This suggests that one or more of the *inv* proteins stimulat signal transduction in the host cell that results engulfment of th salmonellae. A similar invasin gene in*Yersinia* is known to encode a prote that both promotes adherence and activates the cytochalasin-depende

engulfment process. This invasin can confer invasive capacity o
noninvasive *E. coli*, and even latex particle

Intracellular parasites survive inside of phagocytes by virtue
mechanisms which interfere with the bactericidal activities of the host ce
Some of these bacterial mechanisms includ

1. **Inhibition of fusion of the phagocytic lysosomes (granules) wit
the phagosome**. The bacteria survive inside of phagosomes becaus
they prevent the discharge of lysosomal contents into the phagoson
environment. Specifically, phagolysosome formation is inhibited in th
phagocyte. This is the strategy employed by *Salmonella*, *
tuberculosis, *Legionella* and the chlamydia

-With *M. tuberculosis*, bacterial cell wall components (sulfatides) a
thought to be released from the phagosome that modify lysosom
membranes to inhibit fusio

-In *Chlamydia*, some element of the bacterial (elementary body) wa
appears to modify the membrane of the phagosome in which it
containe

-In *L. pneumophila*, as with the chlamydia, some structural feature of th
bacterial cell surface, already present at the time of entry (ingestion
appears to modify the membranes of the phagosomes, thus preventin
their merger with lysosomal granules. In *Legionella*, it is known that
single gene is responsible for the inhibition of phagosome lysosome fusio

-In *Salmonella typhimurium*, the pH that develops in the phagosome aft
engulfment actually induces bacterial gene products that are essential f
their survival in macrophage

2. **Survival inside the phagolysosome**. With some intracellul
parasites, phagosome-lysosome fusion occurs, but the bacteria a
resistant to inhibition and killing by the lysosomal constituents. Also, son
extracellular pathogens can resist killing in phagocytes utilizing simil
resistance mechanisms. Little is known of how bacteria can resi
phagocytic killing within the phagocytic vacuole, but it may be due to th
surface components of the bacteria or due to extracellular substances th
they produce which interfere with the mechanisms of phagocytic killin

Some examples of how certain bacteria (both intracellular an extracellular pathogens) resist phagocytic killing are given belo

-Mycobacteria (including *M. tuberculosis* and *Mycobacterium leprae*) gro inside phagocytic vacuoles even after extensive fusion with lysosome Mycobacteria have a waxy, hydrophobic cell wall containing mycolic aci and other lipids, and are not easily attacked by lysosomal enzyme

-Cell wall components (LPS?) of *Brucella abortus* apparently interfere wi the intracellular bactericidal mechanisms of phagocyte

-B. abortus and *Staphylococcus aureus* are vigorous catalase an superoxide dismutase producers, which might neutralize the toxic oxyge radicals that are generated by the NADPH oxidase and MPO systems phagocytes. *S. aureus*also produces cell-bound pigments (carotenoid that "quench" singlet oxygen produced in the phagocytic vacuol

-The outer membrane and capsular components of Gram-negati bacteria (e.g.*Salmonella*, *Yersinia*, *Brucella*, *E. coli*) can protect th peptidoglycan layer from the lytic activity of lysozym

-Some pathogens (e.g. *Salmonella*, *E. coli*) are known to produ extracellular iron-binding compounds (**siderophores**) which can extra Fe^{+++} from lactoferrin (or transferrin) and supply iron to cells for growt

-Bacillus anthracis resists killing and digestion by means of its capsu which is made up of poly-D-glutamate. The "unnatural" configuration this polypeptide affords resistance to attack by cationic proteins conventional proteases and prevents the deposition of complement on th bacterial surfac

Escape from the phagosome. Early escape from the phagoson vacuole is essential for growth and virulence of some intracellul pathogen

-This is a clever strategy employed by the Rickettsiae. *Rickettsia* ent host cells in membrane-bound vacuoles (phagosomes) but are free in th cytoplasm a short time later, perhaps in as little as 30 seconds. A bacteri enzyme, phospholipase A, may be responsible for dissolution of th phagosome membran

-*Listeria monocytogenes* relies on several molecules for early lysis of th phagosome to ensure their release into the cytoplasm. These include pore-forming hemolysin (listeriolysin O) and two forms of phospholipa C. Once in the cytoplasm, *Listeria* induces its own movement through remarkable process of host cell actin polymerization and formation microfilaments within a comet-like ta

-*Shigella* also lyses the phagosomal vacuole and induces cytoskeletal act polymerization for the purpose of intracellular movement and cell to c sprea

Products of Bacteria that Kill or Damage Phagocyte

One obvious strategy in defense against phagocytosis is direct attack b the bacteria upon the professional phagocytes. Any of the substances th pathogens produce that cause damage to phagocytes have been referre to as**aggressins**. Most of these are actually extracellular enzymes toxins that kill phagocytes. Phagocytes may be killed by a pathogen befo or after ingestio

Killing Phagocytes Before Ingestio

Many Gram-positive pathogens, particularly the pyogenic cocci, secre extracellular substances that kill phagocytes, acting either as enzymes "pore-formers" that lyse phagocyte membrane. Some of these substanc are described as **hemolysins** or leukocidins because of their lethal actio against red blood cells or leukocyte

-Pathogenic streptococci produce **streptolysin**. Streptolysin O binds cholesterol in membranes. The effect on neutrophils is to cause lysosom granules to explode, releasing their lethal contents into the cell cytoplasm

-Pathogenic staphylococci produce **leukocidin**, which also acts on th neutrophil membrane and causes discharge of lysosomal granule

-Extracellular proteins that inhibit phagocytosis include the **Exotox A** of*Pseudomonas aeruginosa* which kills macrophages, and the bacteri exotoxins that are adenylate cyclases (e.g. anthrax toxin EF and pertuss toxin AC) which decrease phagocytic activity through disruption of c equilibrium and consumption of ATP reserves needed for engulfmen

Killing Phagocytes After Ingestion. Some bacteria exert their tox action on the phagocyte after ingestion has taken place. They may gro in the phagosome and release substances which can pass through th phagosome membrane and cause discharge of lysosomal granules, they may grow in the phagolysosome and release toxic substances whi pass through the phagolysosome membrane to other target sites in th cell. Many bacteria that are the intracellular parasites of macrophag (e.g. *Mycobacterium*, *Brucella*, *Listeria*) usually destroy macrophages the end, but the mechanisms are not completely understoo

Other Antiphagocytic Strategies Used by Bacteri

The foregoing has been a discussion of the most commonly-employe strategies of bacterial defense against phagocytes. Although there are fe clear examples, some other antiphagocytic strategies or mechanism probably exist. For example, a pathogen may have a mechanism to inhib the production of phagocytes or their release from the bone marro

A summary of bacterial mechanisms for interference with phagocytes given in the table below

Table 2. BACTERIAL INTERFERENCE WITH PHAGOCYTES

BACTERIUM	TYPE OF INTERFERENCE	MECHANISM
Streptococcus pyogenes	Kill phagocyte	Streptolysin induces lysosomal discharge into cell cytoplasm
	Inhibit neutrophil chemotaxis	Streptolysin is chemotactic repellent
	Resist engulfment (unless Ab is present)	M Protein on fimbriae
	Avoid detection by phagocytes	Hyaluronic acid capsule
Staphylococcus aureus	Kill phagocyte	Leukocidin lyses phagocytes and induces lysosomal

		discharge into cytoplasm
	Inhibit opsonized phagocytosis	Protein A blocks Fc portion of Ab; polysaccharide capsule in some strains
	Resist killing	Carotenoids, catalase, superoxide dismutase detoxify toxic oxygen radicals produced in phagocytes
	Inhibit engulfment	Cell-bound coagulase hides ligands for phagocytic contact
Bacillus anthracis	Kill phagocytes or undermine phagocytic activity	Anthrax toxin EF
	Resist engulfment and killing	Capsular poly-D-glutamate
Streptococcus pneumoniae	Resist engulfment (unless Ab is present)	Capsular polysaccharide
Klebsiella pneumoniae	Resist engulfment	Polysaccharide capsule
Haemophilus influenzae	Resist engulfment	Polysaccharide capsule
Pseudomonas aeruginosa	Kill phagocyte	Exotoxin A kills macrophages; Cell-bound leukocidin
	Resist engulfment	Alginate slime and biofilm polymers
Salmonella typhi	Resist engulfment and killing	Vi (K) antigen (microcapsule)
Salmonella enterica (typhimurium)	Survival inside phagocytes	Bacteria develop resistance to low pH, reactive forms of oxygen, and host

		"defensins" (cationic proteins)
Listeria monocytogenes	Escape from phagosome	Listeriolysin, phospholipase C lyse phagosome membrane
Clostridium perfringens	Inhibit phagocyte chemotaxis	ø toxin
	Inhibit engulfment	Capsule
Yersinia pestis	Resist engulfment and/or killing	Protein capsule on cell surface
Yersinia enterocolitica	Kill phagocytes	Yop proteins injected directly into neutrophils
Mycobacteria	Resist killing and digestion	Cell wall components prevent permeation of cells; soluble substances detoxify of toxic oxygen radicals and prevent acidification of phagolysosome
Mycobacterium tuberculosis	Inhibit lysosomal fusion	Mycobacterial sulfatides modify lysosomes
Legionella pneumophila	Inhibit phagosome-lysosomal fusion	Unknown
Neisseria gonorrhoeae	Inhibit phagolysosome formation; possibly reduce respiratory burst	Involves outer membrane protein (porin) P.I
Rickettsia	Escape from phagosome	Phospholipase A
Chlamydia	Inhibit lysosomal fusion	Bacterial substance modifies phagosome

Brucella abortus	Resist killing	Cell wall substance (LPS?)
Treponema pallidum	Resist engulfment	Polysaccharide capsule material
Escherichia coli	Resist engulfment	O antigen (smooth strains); K antigen (acid polysaccharide)
	Resist engulfment and possibly killing	K antigen

Digestive System Infections **Lec**. 7

Infectious diseases of the Gastrointestinal Tract

Composition and Distribution of the Intestinal Microflora

The intestinal microflora is a complex ecosystem containing over 400 bacterial species. Anaerobes more than facultative anaerobes. The flora is little in the stomach and upper intestine, but excessive in the lower bowel. Bacteria occur both in the lumen and attached to the mucosa, but do not normally penetrate the bowel wall .

The flora also plays a role in fiber digestion and synthesizes certain vitamins. The intestinal microflora synthesizes vitamin K and also synthesize biotin, vitamin B_{12}, folic acid, and thiamine.

- The Intestinal Microflora and Infection

*Protective Activities of the Flora

Like other complex ecosystems, the intestinal microflora is relatively stable over time, maintaining roughly constant numbers and types of bacteria in each area of the bowel. The stability of normal flora both discourages infection by exogenous pathogens and prevents overgrowth of potentially pathogenic members. New organisms that enter the system in contaminated food or water generally are suppressed by the established flora. This suppression is related to production of antimicrobial substances such as bacteriocins or short-chain fatty acids, which inhibit the growth of

alien microorganisms. Antibiotics that kill off part of the intestinal flora can upset its balance and may open the door to infection or pathologic overgrowth.

* Diseases Caused by Overgrowth of Potential Pathogens

The normal intestinal flora includes small populations of organisms that cause disease if they overgrow. For example, overgrowth of *Clostridium difficile* produces severe inflammation of the colon with diarrhea (pseudomembranous colitis). Administration of antibiotics initiates the process by suppressing the normal flora.

- Gastrointestinal infections

1- Esophageal infections:

Viral infections (Herpes), Bacterial infections(T.B, Syphilis), Parasitic infections , Fungal infections(Moniliasis).

2- Gastric diseases : *Helicobacter pylori* Infection:

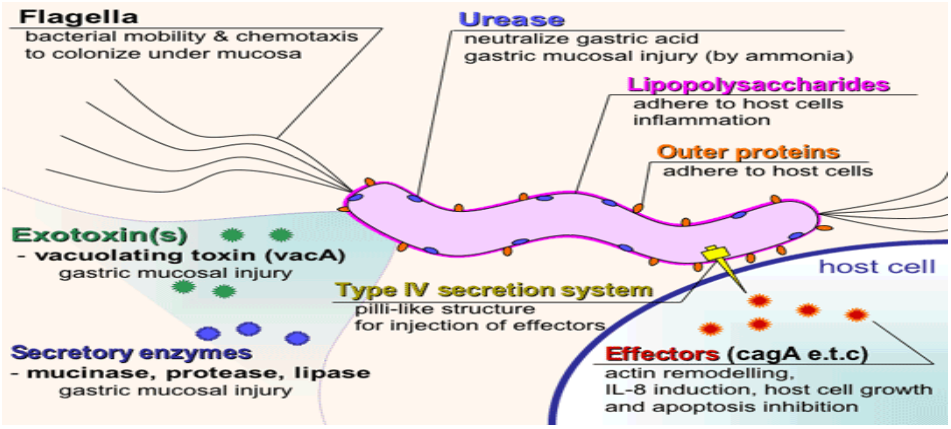
Many people have gastritis, meaning inflammation of the stomach, without even knowing it. Most *Helicobacter pylori* infections are asymptomatic. Early

signs and symptoms may range from belching to vomiting. An infection resulting in ulcers of the stomach or the first part of the small intestine (the duodenum) is marked by localized abdominal pain, tenderness, and bleeding. The ulcers are called peptic ulcers (peptic meaning “caused by digestive juices”). Stomach cancer can also develop.

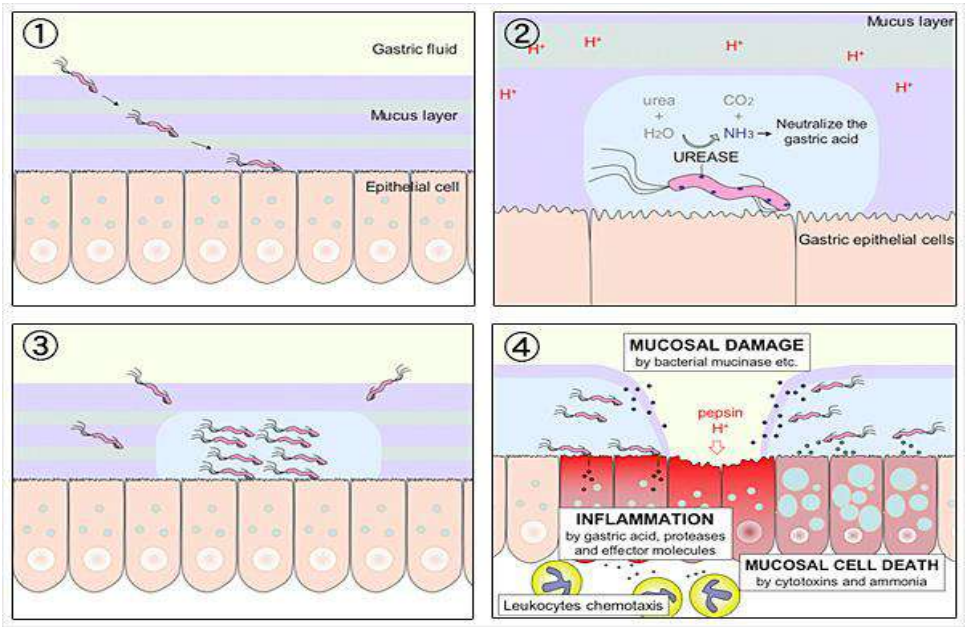
Pathogenesis

Helicobacter pylori cells survive the acidic environment of the stomach by (1) producing urease, an enzyme that converts urea to ammonia, thereby creating an alkaline microenvironment, and (2) burrowing within the mucus layer that coats the stomach lining . Urea is normally found in gastric juices because it is released as proteins are degraded. *H. pylori* cells use their flagella to move through the mucus, following the pH gradient from the acidic gastric lumen to

the nearly neutral underlying epithelial cells. The bacterial cells then attach to the mucus-secreting epithelium or multiply adjacent to it. The ability to both move away from the acidic lumen and produce ammonia from urea are required for *H. pylori* to colonize the stomach.



There are 4 different steps that helicobacter pylori does in order to affect the human host.

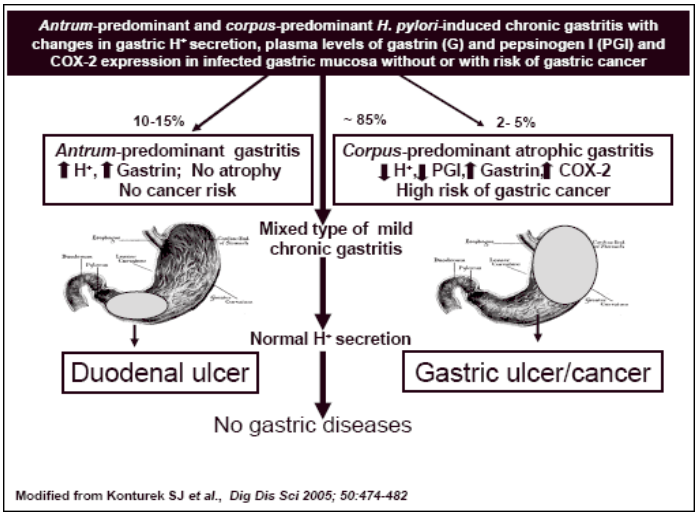


I- Firstly there is the addition of Helicobacter Pylori to the host cell.The addition of helicobacter pylori is enabled by the flagella which allows the bacterium to be motile and also permits the bacteria to propel itself through the gastric fluid, mucus layer and finally adheres itself to the epithelial lipopolysaccharides and membrane proteins, using this it interacts with epithelial cells of stomach.

II- Secondly, and most importantly helicobacter pylori minimizes the content of the acid in the stomach .The hydrochloric acid keeps the pH of the stomach strongly acidic, between a pH of one and two, H.pylori is able to survive in acidic conditions but as the stomach pH is a little too acidic for the bacteria it uses an enzyme to raise the pH around the bacteria to a more survivable level. Urease enzyme is used where it will breakdown urea and water to produce carbon dioxide and ammonia. As we know that ammonia is a base and HCl is an acid this allows a neutralizing reaction making the pH of the stomach increase.

III-Third it colonizes , neutralizing reaction creates a microenvironment for the bacterium to survive this allows the colonization of more and more H. Pylori to thrive in this environment.
IV- Finally it degrades the epithelial cells, the degradation occurs in many different ways:
- The Vac A exotoxin causes injury to the mucosal membrane by inducing alterations in mitochondrial membrane permeability and apoptosis, it also stimulates pro-inflammatory signaling and increases the permeability of the plasma membrane.
- Type IV secretion system uses a pillus to inject effectors such as Cytotoxin-associated gene A - cagA is a needle-like appendage that injects a toxin which remodels actin the cytoskeleton of the cell thereby disrupting the epithelial barrier and facilitating the passage of Vac A, it is also found to inhibit apoptosis.
As the local epithelial cells are damaged due to the combined effects of the *H. pylori* products and the chronic inflammation, mucus production decreases. The thinning of the protective mucus layer and host cell damage probably accounts for the development of peptic ulcers. *H. pylori* infections persist for years, often for life. The outcome of the infection is quite variable. Only about one in six infected persons develops ulcers. A small percentage of chronically infected people develops stomach cancer, but more than 90% of those with stomach cancer are infected.

How helicobacter pylori leads to gastric cancer is not well understood but some ideas are put forward by scientist, it is unclear whether it is one specific cause or a collection of all of these effects of helicobacter pylori which increases the chance of gastric cancer. Long-term exposure to cagA toxin causes chronic inflammation and can induce oncogenesis, this inflammation leads to a damaged mucosal membrane and can increase the carcinogenic effect of risk factors leading to gastric cancer such as high salt intake and smoking. Recent research suggest that cagA may lead to inactivation and alteration of tumor suppressor proteins such as p53 which normally leads to apoptosis and therefore inactivation can promote the development and progression of gastric cancer.* Inflammatory lipid metabolites, prostaglandins, called cyclooxygenases (COXs) bind to specific receptors that activate signaling pathways driving the development and progression of tumors.



3- Intestinal infections

The very common symptom is **Diarrhea**, which is the most common cause of death in developing countries (2.5 million deaths/year).

Diarrheal illness is a common result of bacterial infection of the intestinal tract. Bacteria can also use the intestines as an entry to the rest of the body, thereby causing other types of illness.

General Characteristics

Although many different bacteria can infect the intestinal tract, the diseases they cause share some general characteristics.

The all-too-familiar signs and symptoms of intestinal diseases include diarrhea, loss of appetite, nausea and vomiting, and sometimes fever. The incubation period is typically a day or two, but varies according to the dose consumed. Some physicians often refer to diarrheal disease as **gastroenteritis** (*gastro-*, "stomach," *entero-*, "intestine,"-*itis*, "inflammation"), whereas others prefer the term "stomach flu." ("Stomach flu" has no relationship to "the flu," or influenza.)

Diarrhea can be copious and watery ("the runs") when infection involves the small intestine. Large intestine invasion causes smaller amounts of diarrhea ("the squirts") that contains mucus, pus, and sometimes blood. The name **dysentery** is given to diarrheal illnesses when pus and blood are present

in the feces. A few bacterial pathogens first establish an intestinal infection and then spread systemically. This causes **enteric fever,** characterized by systemic signs such as shock.

Causative Agent

Members of the family *Enterobacteriaceae* are among the most common causes of bacterial diarrhea. These include species of *Shigella* and *Salmonella,* and some strains of *E. coli.* Other causes are *Vibrio cholerae* and *Campylobacter jejuni.* In individuals with predisposing conditions, *Clostridium*

difficile causes diarrhea.

Pathogenesis

The pathogenesis of bacterial intestinal disease involves a number of different mechanisms. Various strains within the same species can differ in the way they cause disease, and the same strain can use more than one mechanism. Moreover, many of the responsible genes are on plasmids, phages, or other mobile genetic elements, which can be transferred from one species to another by horizontal gene transfer.

Attachment to the intestinal surface typically involves adhesins on pili. Additional common mechanisms of pathogenesis include the following:

■ **Toxin production.** Toxins involved in intestinal infections fall into two groups: **enterotoxins,** which cause water and electrolytes to flow from intestinal cells; and **cytotoxins,** which cause cell death. Some types of cytotoxins produced in the intestine can be absorbed into the bloodstream, resulting in systemic effects.

■ **Alterations in intestinal epithelial cells.**

■ **Cell invasion.**

Invasion or cell damage elicits a strong inflammatory response. This primarily occurs in the large intestine and results in the pus and blood in the feces that characterize dysentery.Proteins injected by type III secretion systems can also elicit an inflammatory response.

I- Bacterial Gastroenteritis

-*Escherichia coli* Gastroenteritis

Escherichia coli strains are almost universal residents of the intestinal tracts of humans and a number of other animals. Although most strains are harmless, certain ones produce specific virulence factors that allow them to cause intestinal disease. The incubation periods, signs, symptoms, and severity of

E. coli gastroenteritis depend on the infecting strain. Some strains cause watery diarrhea and others cause dysentery. One group can cause hemolytic uremic syndrome (HUS), marked by anemia due to lysis of red blood cells and kidney failure.

Pathogenesis

Escherichia coli strains that cause intestinal disease can be grouped into six pathovars (pathogenic varieties), based on their array of virulence factors.

■ **Enterotoxigenic E. coli (ETEC)** - infantile diarrhea and Traveler's diarrhea. ETEC strains colonize the small intestine and produce a cholera-like (heat-labile; LT) toxin and a heat stable toxin (ST). Both toxins ultimately stimulate the secretion of chloride by the host cells resulting in

a watery diarrhea. The genesmfor adhesin and toxin synthesis are on plasmids.

■ **Enteropathogenic E. coli (EPEC)**- diarrhea in infants less than 6 months of age. EPEC produces no demonstrable toxin. They cause what is termed an attaching-and-effacing(A/E) histopathology in the small intestine.

■ **Shiga toxin–producing *E. coli* (STEC).** These strains, also referred to as EHEC or enterohemorrhagic *E. coli,* produce Shiga toxins, a family of functionally identical toxins that includes the toxin of *Shigella dysenteriae.* In
STEC strains, the genes for Shiga toxins are encoded by various related prophages, an example of lysogenic conversion. Some STEC strains produce multiple types of Shiga toxins, and even make other toxins as well. Most of the strains identified in outbreaks belong to a single serotype, O157:H7, but there are important exceptions. STEC strains typically colonize the large intestine, where they inject effector proteins that cause attaching and effacing (A/E) lesions. The intestinal damage results in diarrhea, which becomes bloody (hemorrhagic diarrhea) due to the action of Shiga toxins on the local blood vessels.
About 5% to 10% of people infected with STEC develop hemolytic uremic syndrome (HUS). The STEC strain that caused the 2011 outbreak in Europe (serotype O104:H4) is unusual because it does not produce A/E lesions and has
characteristics of the EAEC pathovar.

■**Enteroinvasive *E. coli* (EIEC).** These strains invade the intestinal epithelium, causing a disease similar to shigellosis.

■Enteroaggregative E. coli (EAEC)- These strains produce pili that allow them to adhere to the intestinal epithelium. There, they grow in characteristic aggregations in a thick mucus-associated biofilm. In addition, they produce enterotoxins and cytotoxins, damaging the intestinal cells and evoking an inflammatory response.
a major cause of Traveler's diarrhea, a more persistent diarrhea . EAEC involves three stages that include;
1. Adherence to the mucosa
2. Enhanced mucus production that encases the bacteria forming a biofilm
3. Followed by elaboration of a cytotoxin, which damages the intestinal cells.

…Diffusely adhering E.coli (DAEC) .these strains are similar to EAEC .but rather than forming aggregations,the grow as a diffuse layer .

- Vibrio

Cholera is endemic in India, Bangladesh and Louisiana in the U.S. The organism is ingested with water or food (especially shellfish and crabs) and causes an acute illness due to an enterotoxin elaborated by *V. cholerae* that have colonized the small bowel. In its most severe form, there is rapid loss of liquid and electrolytes from the gastrointestinal tract, resulting in shock, metabolic acidosis if untreated.

Cholera- The onset is characterized by watery diarrhea. Several liters of liquid may be lost within a few hours, rapidly leading to profound shock. Vomiting may ensue after diarrhea.

-Antimicrobic-associated pseudomembranous colitis

Antibiotic-associated diarrhea develops in up to 30% of hospitalized patients. *Clostridium difficile* is a bacterium that is resistant to most broad-spectrum antibiotics. It is present in the intestine of about 5% of humans. Long-term systemic antibiotic therapy reduces the number of viable bacteria in the intestine but allows *C. difficile* to become the predominate organism in the GI tract. *C. difficile* releases toxins that may cause bloating and diarrhea, with abdominal pain, which may become severe .The organism produces small amounts of toxin A(enterotoxin) and toxin B(cytotoxin), which only achieve cytotoxic levels when it is the predominant organism, enterotoxins that cause areas of necrosis in the wall of the intestine .

Pathogenesis

When antibiotics have disrupted the normal microbiota in the large intestine, creating an imbalanced condition called dysbiosis, *C. difficile* can proliferate. Pathogenic *C. difficile* strains release toxins that result in a variety of signs and symptoms, including diarrhea. At least two toxins (toxin A and toxin B) appear to cause symptoms in *Clostridium difficile* infection (CDI). Both toxins are A-B toxins that disrupt regulation of host cell actin polymerization and various other signaling pathways, causing lethal effects to the intestinal epithelium.

The toxins also cause macrophages to release proinflammatory cytokines, inducing a strong inflammatory response. In some cases, the net result is formation of pseudomembranes composed of dead epithelium, inflammatory cells, and clotted blood on the inner wall of the intestine. A third toxin, sometimes called binary toxin because it is composed of separate proteins, is produced by the hypervirulent strains. Like toxins A and B, this toxin also interferes with actin polymerization.

Signs and symptoms range from mild diarrhea to severe life threatening inflammation of the colon.

-Watery diarrhea- most common symptomatic disease is watery diarrhea (5-15 stools per day). Symptoms include abdominal pain that decreases after bowel movements, low-grade fever, and mild peripheral blood leukocytosis. Usually the diarrhea begins 5-10 days after antibiotics are started. However, symptoms may be delayed as long as 10 weeks after completion of antibiotic therapy.
-Pseudomembranous colitis- The colon is inflamed and gradually sloughs off loose, membrane like patches called pseudomembranes consisting of inflammatory cells, fibrin, and necrotic cells , pseudomembranes observed by colonoscopy.
-Fulminant colitis- Fulminant (sever and sudden) colitis (inflammation of the large intestine). Severity appears to be related to the number of receptors for the bacterial toxin on the colon, develops in 2-3% of patients. This disease has a severe morbidity and high mortality
-Toxic megacolon- persistent high fever, marked leukocytosis, lack of response to antibiotics and marked bowel thickening on CT scan.

-Campylobacteriosis
Campylobacteriosis is an infection of the gastrointestinal tract. Symptoms of the infection include diarrhoea (often including the presence of mucus and blood), abdominal pain, malaise, fever, nausea and vomiting. The illness usually lasts 2 to 5 days but may be prolonged by relapses, especially in adults.
Many of those infected show no symptoms. In some individuals a reactive arthritis (painful inflammation of the joints) can occur.

Campylobacter jejuni is the most common cause of gastroenteritis worldwide , gram-negative, comma-shaped rods **.** Some strains of *C jejuni* produce a cholera-like enterotoxin, which is important in the watery diarrhea observed in infections. The organism produces diffuse, bloody, edematous, and exudative enteritis**.**

Pathogenesis
Once ingested, *Campylobacter jejuni* passes through the stomach and penetrates the epithelial cells of the small and large intestines. The bacteria multiply within and beneath the epithelium and cause a localized inflammatory reaction. Penetration into the bloodstream is uncommon. A mysterious consequence of *C. jejuni* infection, Guillain-Barré syndrome, occurs in about 0.1% of cases. Up to 40% of all Guillain-Barré cases are preceded by campylobacteriosis, and autoimmunity is likely involved. The syndrome begins within about 10 days of the onset of diarrhea, with tingling of the feet followed by progressive paralysis of the legs, arms, and

rest of the body. Most patients require hospitalization, but recover completely; about 5% of patients die despite treatment.

-Shigellosis

Shigellosis is found all over the world, most commonly in areas lacking adequate sewage treatment. Shigellosis has an incubation period of 1 to 3 days. It classically involves dysentery, but some *Shigella* species cause watery diarrhea. Other signs and symptoms include headache,vomiting, fever, stiff neck, and joint pain. The disease is often fatal for infants in developing countries. Shigella are transmitted through a fecal-oral route, they are well adapted to colonize and reproduce in the colon . The main target of Shigella is the colonic epithelium . The bacterium's virulence is determined/encoded by plasmids . The determinants are plasmid encoded and are designated as Invasion Plasmid Antigens (Ipa) B and C . These Ipa determinants are expressed in the bacteria when under specific conditions of bile salts, high osmolarity, human body temperature etc. Making the environment of the colon ideal for the bacterium to colonize .

Causative Agent

Shigellosis is caused by the four species of *Shigella — S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei.* Of these,*S. dysenteriae* is the most virulent, and *S. sonnei* the least. Shigellosis in developing countries is typically caused by *S. dysenteriae* and *S. flexneri.* In the United States, however, *S. sonnei* causes over two-thirds of the cases. Like other members of the family *Enterobacteriaceae, Shigella* species are Gram-negative rods.

Pathogenesis

Shigella species invade intestinal epithelial cells, causing a strong inflammatory response. To initiate invasion, the bacteria take advantage of the antigen sampling function of microfold cell(M cells), which normally transfer microbes to macrophages in Peyer's patches. Once the bacterium makes contact with the colonic epithelium, it is triggered to release its IpaB and IpaC complexes . These complexes then induce the uptake of the bacterium by epithelial cells and macrophages . Once *Shigella* cells enter the macrophages, they escape from the phagosome and multiply in the macrophages' cytoplasm. These hidden bacteria are released when the infected macrophages die. With access to the bases of the intestinal epithelial cells, *Shigella* cells attach to specific receptors and induce the epithelial cells to take them in. Once inside, the *Shigella* cells escape into the cytoplasm of epithelial cells, where they multiply. Although nonmotile, the bacterial cells produce a protein called Intercellular Spread protein (IcsA) that induces the polymerization of actin. This "actin tail" propels the bacterium within the cell, sometimes with enough force to move it into a neighboring cell. The overall result of invasion and spread is the death

and sloughing of patches of epithelium. The bare areas become intensely inflamed, covered with pus and blood, which accounts for the signs and symptoms of dysentery.

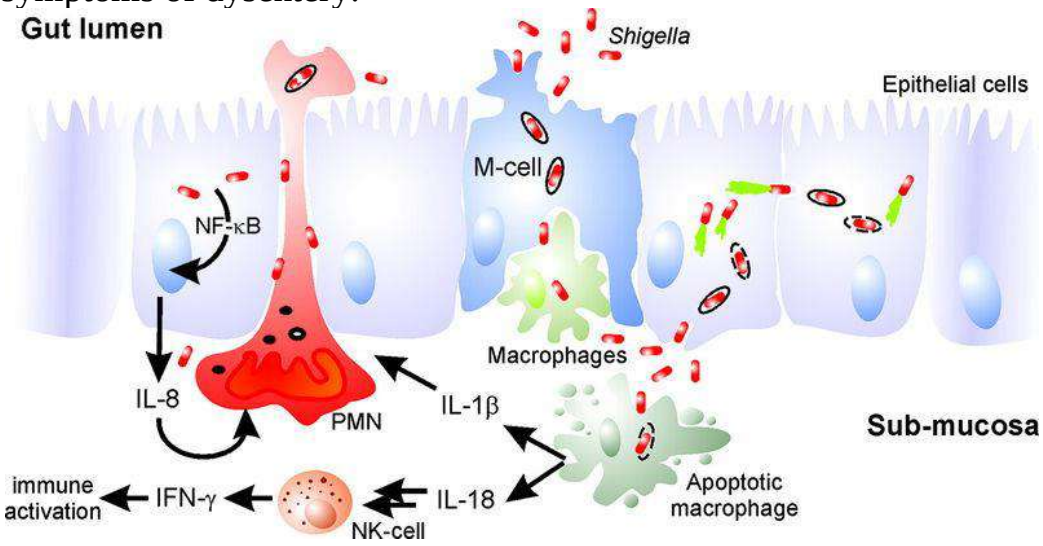


Figure : **Pathogenesis of *Shigella***

Some strains of *Shigella dysenteriae* produce a potent cytotoxin known as Shiga toxin, a chromosomally encoded A-B toxin. The toxin enters the bloodstream and then the B portion binds to endothelial cells that line the small blood vessels, particularly in the kidneys. This allows the A subunit to then enter the cells, where it reacts with ribosomes, halting protein synthesis, which leads to cell death. Shiga toxin is important because it is responsible for **hemolytic uremic syndrome (HUS),** an often fatal condition that can follow
Shigella dysenteriae infection. In HUS, red blood cells break up in the tiny blood vessels, resulting in anemia and kidney failure. Symptoms of HUS sometimes include paralysis or other signs of nervous system injury. Shiga toxin is also produced by strains of *Escherichia coli* that cause HUS.

-Salmonellosis

It is an infection caused by Salmonella bacteria. Most people infected with *Salmonella* develop diarrhea, fever ,vomiting ,and abdominal cramps 12 to 72 hours after infection. In most cases, the illness lasts four to seven days, and most people recover without treatment. In some cases, the diarrhea may be so severe that the patient becomes dangerously dehydrated and must be hospitalized.

***Salmonella* gastroenteritis**

Salmonella gastroenteritis is caused by numerous serotypes of *Salmonella enterica* and can be acquired from many animal sources. Signs and symptoms of *Salmonella* gastroenteritis include diarrhea (sometimes bloody), abdominal cramps, nausea, vomiting, headache, and fever. The disease is often short-lived and mild, but that varies depending on the virulence of the infecting strain and the number of cells ingested. Similarly, the incubation period varies from 6 hours to 3 days.

Causative Agent

Salmonella enterica is a Gram-negative rod , a member of the *Enterobacteriaceae.* The various *Salmonella* strains are subdivided into more than 2,400 serotypes based on differences in their somatic (O), flagellar (H), and capsular (K) antigens. Each serotype was once considered a separate species and given a distinct name. However, DNA sequence data indicates there are only two species— *S. enterica* and *S. bongori,* the latter only rarely isolated from humans.

Salmonella pathogenicity islands (SPI), historically acquired through horizontal gene transfer events, include clusters of genes, which encode the mechanisms through which *Salmonella* acts as a virulent pathogen . These genetic islands are located on the bacterial chromosome or on plasmids, however, not all serovars possess every known SPI. SPI-1 through SPI-5 are common among all *S. enteric* serovars . 23 SPI have been described although the functions of those genes contained within each island have not yet been completely elucidated . SPI-1 and SPI-2 are of particular importance in *in vivo* infection.

Pathogenesis

Most Salmonella serotypes are sensitive to acid, so millions of cells must generally be ingested for enough to survive passage through the stomach to colonize the intestines, some of the bacterial cells attach to specific receptors on the surface of the epithelial cells. SPI-1 genes are expressed encoding T3SS-1 which transfers bacterial effector proteins into the epithelial cell. Within minutes, the epithelial cell takes in the bacterial cells by endocytosis. After being internalized by macrophages, *Salmonella* then reside within a membrane bound compartment distinct from the phagosome and lysosome known as the *Salmonella*-containing vacuole (SCV), Figure 6 . In this cellular compartment , *Salmonella* can survive and replicate in the absence of host antimicrobial defense mechanisms , thereby evading endosomal fusion with the NADPH oxidase complex . From within the SCVs, SPI-2 genes are expressed encoding T3SS-2, which enables *Salmonella* to translocate a range of effector proteins into the cytoplasm of the host cell leading to the rearrangement of the actin cytoskeleton.

The bacteria multiply within a phagosome and are discharged from the base of the cell by exocytosis. Some bacterial cells escape the phagosome and multiply in the cytoplasm. Macrophages and neutrophils take up any bacteria that are released, but the macrophages are often destroyed as a result, invasion of the mucosa causes the epithelial cells to synthesize and release various proinflammatory cytokines, including: IL-1, IL-6, IL-8, TNF-α and IFN-γ. These evoke an acute inflammatory response and may also be responsible for damage to the intestine. The infection, however, remains localized. The inflammatory response increases epithelial cell fluid secretion, causing diarrhea by activation of mucosal adenylate cyclase; the resultant increase in cyclic AMP induces secretion. The mechanism by which adenylate cyclase is stimulated is not understood; it may involve local production of prostaglandins or other components of the inflammatory reaction. In addition, *Salmonella* strains elaborate one or more enterotoxin-like substances which may stimulate intestinal secretion. However, the precise role of these toxins in the pathogenesis of *Salmonella* enterocolitis and diarrhea has not been established.

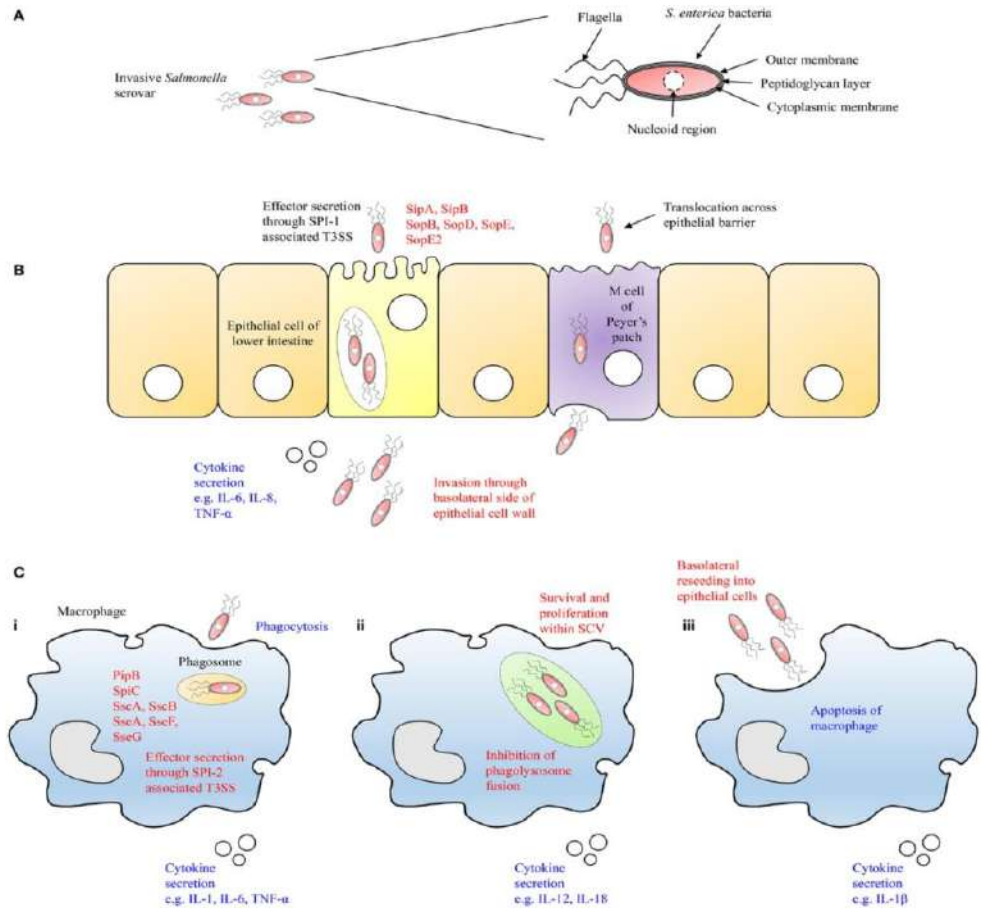


Figure 6. Schematic illustration of the infection of epithelial cells of the lower intestine and macrophages by *Salmonella* is shown.
(A) The complex membrane structure of *Salmonella* allows it to survive until reaching the epithelial cell wall of the host in the lower intestine.(B) *Salmonella* then translocate across

M cells of Peyer's patches or actively invade epithelial cells by the secretion of effector proteins through the SPI-1 encoded T3SS-1. (C) (i) After crossing the epithelial barrier, *Salmonella* are engulfed by proximal macrophages that will secrete effector proteins into the cytosol of the cell via the SPI-2 encoded T3SS-2 and prevent fusion of the phagosome with the lysosome. (ii) Within the SCV, *Salmonella* will proliferate resulting in cytokine secretion by the macrophage. (iii) Finally, the macrophage will undergo apoptosis, and *Salmonella* will escape the cell to basolaterally reinvade epithelial cells or other phagocytic cells of the host innate immune system.

Typhoid fever:

Typhoid fever and paratyphoid fever are enteric fevers— systemic diseases that originate in the intestine. They are caused by specific serotypes of *Salmonella enterica* and spread from person to person through fecal-oral transmission. Following an incubation period of 1 to 3 weeks, patients develop a progressively increasing fever over several days, severe headache, constipation, and abdominal pain. In severe cases, this is followed by intestinal rupture, internal bleeding, shock, and death.These are systemic diseases, so cases are confirmed by blood culture rather than stool culture.

Pathogenesis

Bacteria that cause enteric fever colonize the intestines, cross the mucous membrane via M cells, and then resist killing by macrophages. After multiplying within macrophages, the bacteria are carried in the bloodstream to locations throughout the body. The systemic infection causes fever, abscesses, sepsis (a systemic inflammatory response due to bloodstream infection), and shock, often with little or no diarrhea. The Peyer's patches are sometimes destroyed, leading to rupture of the intestine, hemorrhage, and death. A little is known about the bacterial mechanisms that lead to enteric fever, but researchers have recently identified a toxin (typhoid toxin) that is only produced by the bacterial cells when they are within a host cell. The role of this toxin in the disease process is still being studied.

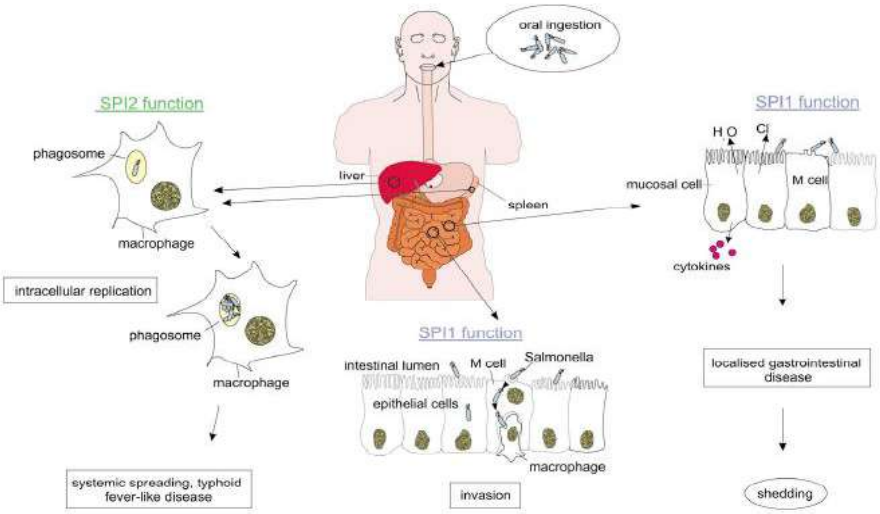


Figure . Schematic representation of host–pathogen interactions during pathogenesis of *Salmonella* infections. *Salmonella* Pathogenicity Island (SPI1) function is required for the initial stages of salmonellosis, i.e. the entry of *Salmonella* into non- phagocytic cells by triggering invasion and the penetration of the gastrointestinal epithelium. Furthermore, SPI1 function is required for the onset of diarrhoeal symptoms during localized gastrointestinal infections. The function of SPI2 is required for later stages of the infection, i.e. systemic spread and the colonization of host organs. The role of SPI2 for survival and replication in host phagocytes appears to be essential for this phase of pathogenesis.

Respiratory Tract Infections Lec 8

Infections of the upper respiratory system are the most common type of infection. Pathogens that enter the respiratory system can infect other parts of the body.

Normal Microbiota of the Respiratory System

The normal flora of the nasal cavity and throat can include pathogenic microorganisms**.**

Nasal Cavity: Diphtheroids , Staphylococci , Micrococci & *Bacillus* species

Throat: *Streptococcus pneumonia* , *Haemophilus influenza* & *Neisseria meningitidis*

The microbiota of the respiratory tract has two main functions important in maintaining the healthy state of the host: (1) These organisms compete with pathogenic organisms for potential attachment sites, and (2) they can produce substances that are bactericidal and prevent infection by pathogens.

The lower respiratory system is usually sterile because of the action of the ciliary escalator. However, recent studies have shown that there are from 10-100 bacterial cells per 1000 lung cells. Many of the organisms in the lower respiratory tract microbiota do not grow on media commonly used to grow bacteria. It appears that most of the lung microbiota comes from the oropharynx.

Pathogenic organisms inhaled or aspirated into the lower respiratory tract are usually eliminated by alveolar macrophages. To protect themselves from the alveolar macrophages most pathogenic bacteria (e.g., *Streptococcus pneumoniae, Klebsiella pneumonia* and *Haemophilus influenzae*) produce a capsule that inhibits phagocytosis. Other pathogenic microorganisms escape alveolar macrophage killing by reproducing/surviving **in the cells that line the respiratory tree** (e.g., Influenza virus) or by reproducing/surviving **in the alveolar macrophages** (e.g., *Mycobacterium tuberculosis*).

Microbial Diseases of the Upper Respiratory System

Specific areas of the upper respiratory system can become infected to produce pharyngitis, laryngitis, tonsillitis, sinusitis, and epiglottis.
These infections may be caused by several bacteria and viruses, often in combination.
Most respiratory tract infections are self-limiting.
H. influenzae type b can cause epiglottitis.

Bacterial Diseases of the Upper Respiratory System

Streptococcal Pharyngitis (Strep Throat) and tonsillitis

Caused by *S. pyogenes* (group A beta-hemolytic streptococcus). *S. pyogenes* is resistant to phagocytosis and produces streptokinase, DNAse and hemolysins.
Symptoms are inflammation of the mucous membrane and fever; tonsillitis and otitis media may also occur.
Preliminary rapid diagnosis by indirect agglutination tests. Definitive diagnosis is based on a rise in IgM antibodies.

Pathogenesis and Clinical Manifestations

Bacteria attach to and, in the case of group A beta-hemolytic streptococci, invade the mucosa of the upper respiratory tract. Many clinical manifestations of infection appear to be due to the immune reaction to

products of the bacterial cell. In diphtheria, a potent bacterial exotoxin causes local inflammation and cell necrosis.
Pharyngitis usually presents with a red, sore, or “scratchy” throat. An inflammatory exudate or membranes may cover the tonsils and tonsillar pillars. Vesicles or ulcers may also be seen on the pharyngeal walls. Anterior cervical lymphadenopathy is common in bacterial pharyngitis and difficulty in swallowing may be present.

Diphtheria
Diphtheria is caused by an exotoxin-producing gram-positive rod, *Corynebacterium diphtheriae*. A potent exotoxin is produced when the bacteria are lysogenized by a phage. Pseudomembrane formation occurs in the throat. The membrane contains fibrin and dead host and bacterial cells and can block the passage of air.

Diphtheria Membrane

The exotoxin inhibits protein synthesis and may damage the heart, kidney and/or nerves.Laboratory diagnosis is based on isolation and identification.
Treatment: Administer antitoxin to neutralize the toxin and antibiotics to stop growth of the bacteria.
Prevention: Immunization with DPT.
Cutaneous diphtheria is characterized by slow healing skin ulcerations.
There is minimal dissemination of exotoxin in the bloodstream.

Viral Diseases of the Upper Respiratory System

The Common Cold (Rhinitis)
Caused by any one of around 200 viruses; rhinoviruses are the most common cause (about 50%).
Symptoms include sneezing, nasal secretions, and congestion.
Complications include sinus infections, lower respiratory tract infections, laryngitis, and

Pathogenesis and Clinical Manifestations

The viruses appear to act through direct invasion of epithelial cells of the respiratory mucosa , but whether there is actual destruction and sloughing of these cells or loss of ciliary activity depends on the specific organism involved. There is an increase in both leukocyte infiltration and nasal secretions, including large amounts of protein and immunoglobulin, suggesting that cytokines and immune mechanisms may be responsible for some of the manifestations of the common cold .

After an incubation period of 48–72 hours, classic symptoms of nasal discharge and obstruction, sneezing, sore throat and cough occur in both adults and children. headache may also be present. Fever is rare. The duration of symptoms and of viral shedding varies with the pathogen and the age of the patient.

A complication of acute viral upper respiratory illness

Otitis externa : is characterized by inflammation of the ear canal, with purulent ear drainage. It can be quite painful, and cellulitis can extend into adjacent soft tissues. A common form is associated with swimming in water that may be contaminated with aerobic Gram negative organisms such as *Pseudomonas* species.

Otitis Media

Often a complication of nose and throat infections but can also be caused by direct inoculation.

Pus accumulation causes pressure on the tympanic membrane.

Common bacterial causes:

Streptococcus pneumonia , Haemophilus influenza , Klebsiella pneumoniae,

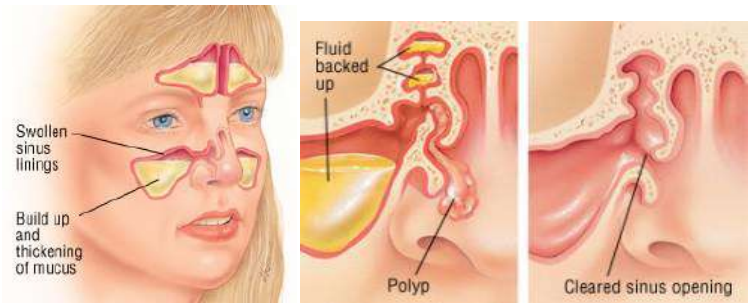
Moraxella catarrhalis , Streptococcus pyogenes & *Staphylococcus aureus*

Sinusitis

Sinusitis is an acute inflammatory condition of one or more of the paranasal sinuses.

Acute sinusitis most often follows a common cold which is usually of viral etiology. allergic rhinitis may also be progressed to the development of sinusitis. The most common bacterial agents responsible for acute sinusitis are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. Other organisms including *Staphylococcus aureus, Streptococcus pyogenes,* gram-negative organisms and anaerobes have also been recovered. Chronic sinusitis is commonly a mixed infection of aerobic and anaerobic organisms.

Pathogenesis and Clinical Manifestations
Infections caused by viruses or bacteria impair the ciliary activity of the epithelial lining of the sinuses and increased mucous secretions. With bacterial multiplication in the sinus cavities, the mucus is converted to mucopurulent exudates. The pus further irritates the mucosal lining causing more edema, epithelial destruction and ostial obstruction. When acute sinusitis is not resolved and becomes chronic, mucosal thickening of mucus results and polyps may developed.
In uncomplicated chronic sinusitis, a purulent nasal discharge is the most constant finding. There may not be pain nor tenderness over the sinus areas.



Bacterial Diseases of the Lower Respiratory System

Many of the same microorganisms that infect the upper respiratory system also infect the lower respiratory system.

Diseases of the lower respiratory system include bronchitis and pneumonia.

Pertussis (Whooping Cough)
Caused by *Bordetella pertussis*, which produces a very potent exotoxin.
The initial stage, or the catarrhal stage, presents like a cold.
The second, or paroxysmal stage, is characterized by mucus accumulations in the trachea and bronchi, which cause deep coughing.
The third, or convalescence stage, can last for months.
Prevention: Immunization with DPT

Tuberculosis
Caused by *Mycobacterium tuberculosis*.
The bacterium is acid-fast due to lipid in the cell wall, which makes it very resistant to drying and disinfectants.

The lipid fraction of M.TB's cell wall consists of three major components.
-Mycolic acids (50%) they prevent attack of the mycobacteria by cationic

proteins, lysozyme and oxygen radicals in the phagocytic granule. They also protect extracellular mycobacteria from complement deposition in serum.

- **Cord Factor** is responsible for the serpentine cording mentioned above. Cord factor is toxic to mammalian cells and is also an inhibitor of PMN migration. Cord factor is most abundantly produced in virulent strains of M.TB.

Wax-D in the cell envelope is the major component of **Freund's complete adjuvant** (CFA).

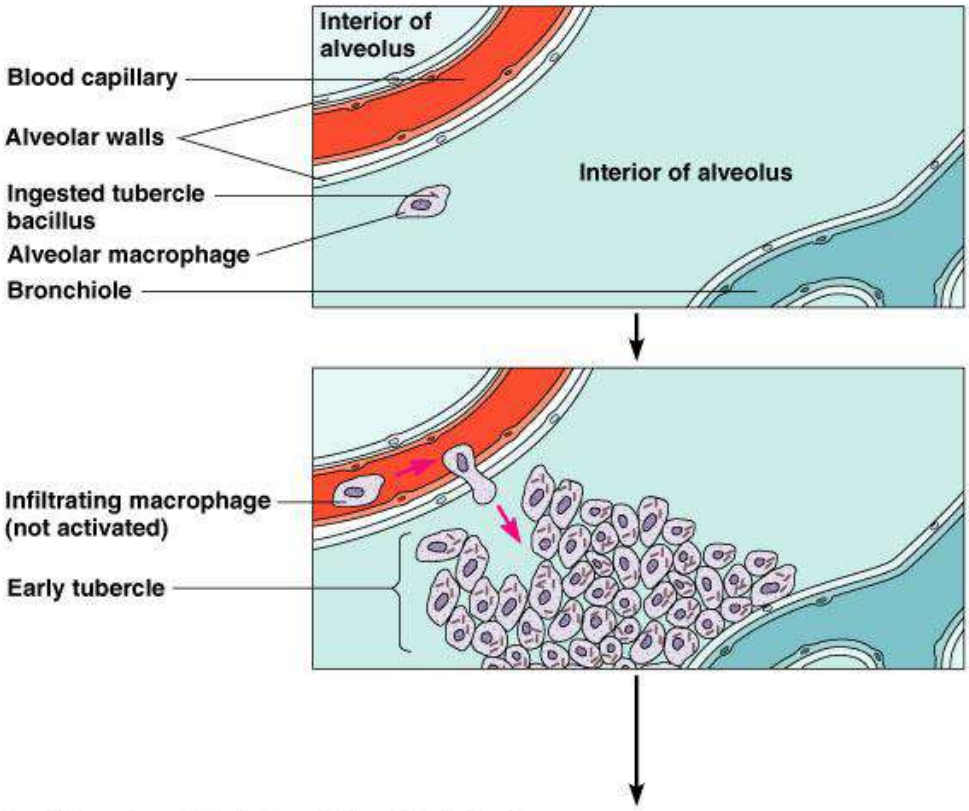
Filamentous fungus-like growth caused by cord factor

The bacteria may survive phagocytosis and may reproduce in macrophages. Transmission is by droplet nuclei (respiratory aerosols).

Lesions are called tubercles; dead macrophages and bacteria form caseous lesions that may calcify and appear on X ray as a Ghon complex.Liquefaction of the caseous lesion results in a tuberculous cavity in which *M. tuberculosis* can grow.

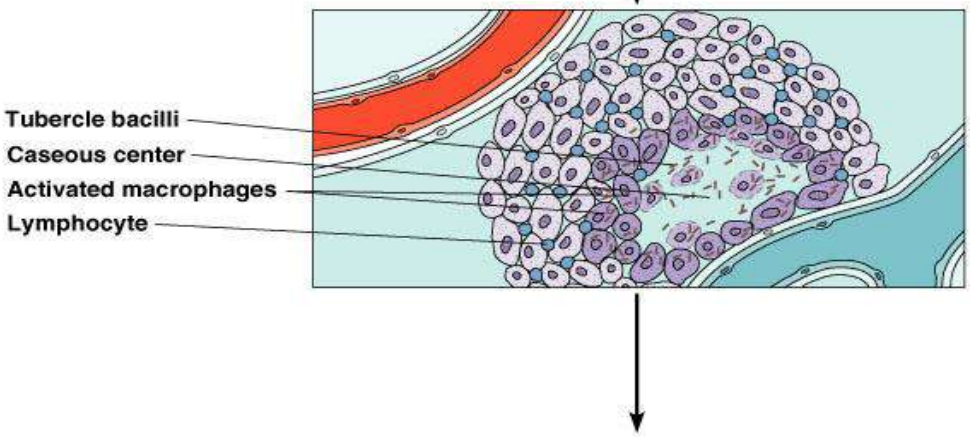
Small metastatic foci containing low numbers of M.TB. may also calcify. However, in many cases these foci will contain viable organisms. These foci are referred to **Simon foci**.

Pathogenesis of Tuberculosis

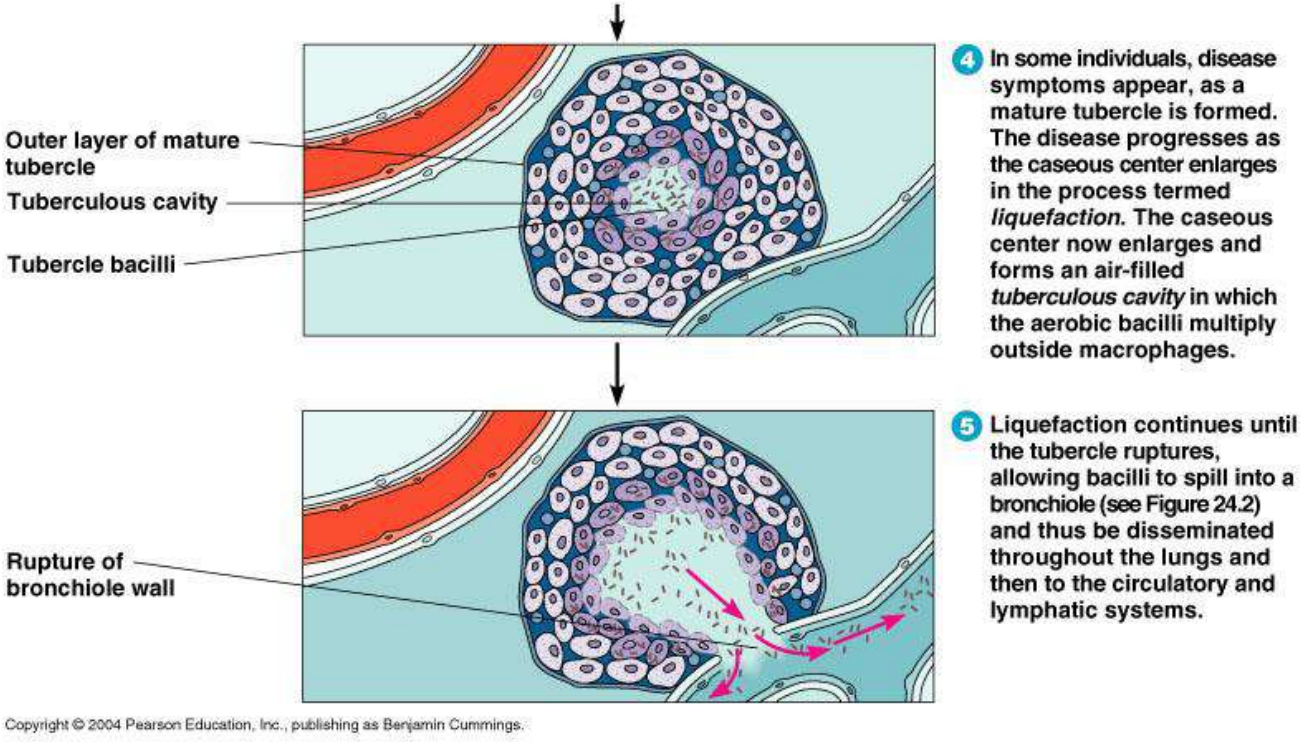


1 Tubercle bacilli that reach the alveoli of the lung (Figure 24.2) are ingested by macrophages, but some often survive. Infection is present, but no symptoms of disease.

2 Tubercle bacilli multiplying in macrophages cause a chemotactic response that brings additional macrophages and other defensive cells to the area. These form a surrounding layer and, in turn, an early tubercle. Most of the surrounding macrophages are not successful in destroying bacteria but release enzymes and cytokines that cause a lung-damaging inflammation.



3 After a few weeks, disease symptoms appear as many of the macrophages die, releasing tubercle bacilli and forming a *caseous center* in the tubercle. The aerobic tubercle bacilli do not grow well in this location. However, many remain dormant (latent TB) and serve as a basis for later reactivation of the disease. The disease may be arrested at this stage, and the lesions become calcified.



New foci of infection can develop when a caseous lesion ruptures and releases bacteria into blood or lymph vessels; this is called miliary tuberculosis. Miliary tuberculosis is characterized by weight loss, coughing, and loss of vigor.

A positive tuberculin test is used to determine previous exposure; it is not diagnostic because a positive test may indicate an active case, a previous infection, or vaccination and immunity.

Laboratory diagnosis is based on isolation and identification - takes up to 8 weeks.

Mycobacterium bovis causes bovine tuberculosis and can be transmitted to humans by unpasteurized milk. *M. bovis* infections usually affect the bones or lymphatic system.

Pneumonia

Pneumonia is an inflammation of the lungs that is usually caused by infection. With pneumonia, the air sacs in the lungs fill with liquid or pus, which interferes with the lungs' ability to transfer oxygen to the blood.
There are many different kinds of pneumonia, ranging from mild to severe. There are 4 basic types:

1- Community-acquired pneumonia (CAP), the most common type of pneumonia, is caused by bacteria, viruses, and other organisms that are acquired outside of the hospital or other health care settings.

2- Hospital-acquired pneumonia (HAP) occurs at least 48 hours after someone has been admitted to the hospital. It can be caused by bacteria and other organisms that are usually different from CAP. HAP is usually more serious than CAP because the bacteria and organisms can be harder to treat, and because people who get HAP are already sick.

3- Aspiration pneumonia occurs when liquids or other irritants are inhaled into the lungs. The most common type of aspiration pneumonia is caused by inhaling stomach contents after vomiting. People with medical problems that affect swallowing are at an increased risk of this type of pneumonia. Aspiration pneumonia from anaerobic organisms usually occurs in patients with periodontal disease . The bacteria involved are usually part the oral flora and cultures generally show a mixed bacterial growth. *Actinomyces, Bacteroides, Peptostreptococcus, Veilonella, Propionibacterium, Eubacterium*, and *Fusobacterium* spp are often isolated.

4- Opportunistic pneumonia occurs in people with weakened immune system (e.g., people with AIDS, cancer, organ transplant). Organisms that are not usually harmful to people with healthy immune systems cause these types of infections.

Bacterial Pneumonias
Mostly caused by normal flora from the mouth and throat. The most common causes are: *Streptococcus pneumonia ,Haemophilus influenza , Staphylococcus aureus , Legionella pneumophila & Mycoplasma pneumoniae*

Typical pneumonia is caused by *S. pneumoniae*.
Atypical pneumonias are caused by other microorganisms.

Pneumococcal Pneumonia
Pneumococcal pneumonia is caused by encapsulated *Streptococcus pneumoniae*.
Symptoms are rust colored sputum, fever, difficult breathing, and chest pain.
The lungs have reddish appearance due to dilation of blood vessels. Alveoli fill with erythrocytes and fluid.

Initial diagnosis is made by X-rays. Laboratory diagnosis is by isolation and identification based on production of alpha-hemolysins, inhibition by optochin, bile solubility, and through serological tests.

The treatment of choice is penicillin.
A purified capsular vaccine consisting of capsular material from 23 serotypes of *S. pneumoniae* is available.

Haemophilus influenzae Pneumonia
Alcoholism, poor nutrition, cancer, and diabetes are predisposing factors for *H. influenzae* pneumonia.

H. influenzae is a gram-negative coccobacillus.

Mycoplasmal Pneumonia
Mycoplasmal pneumonia (primary atypical pneumonia or walking pneumonia) is caused by the pleomorphic rod *Mycoplasma pneumoniae*.
Mycoplasma pneumoniae produces characteristic fried egg colonies after 2 weeks' incubation on enriched media containing horse serum and yeast extract.
Symptoms are low grade fever, cough, and headache. Mortality rate is less than 1%.
Diagnosed by PCR or complement fixation.
The treatment of choice is tetracycline or erythromycin.

Legionellosis
Caused by the aerobic gram-negative rod *Legionella pneumophila*. Two very different kinds of respiratory illness may result from infection. The most common presentation is acute pneumonia, which varies in severity from mild illness that does not require hospitalization (**walking pneumonia**) to fatal multilobar pneumonia. Most patients respond to appropriate antimicrobial therapy, but convalescence is often prolonged (lasting many weeks or even months).

The second form of respiratory illness is called **Pontiac fever** after the city in Michigan where the first epidemic was recognized. This uncommon manifestation of infection resembles acute influenza, including fever, headache, and severe muscle aches. It is self-limited. Bacteremia occurs during *Legionella* pneumonia.

The organism grows in water and is spread through the air; it is resistant to chlorine.Person to person spread is not likely. High risk groups are males over 50, heavy smokers, alcohol abusers, and those with chronic illness.

Infection begins in the lower respiratory tract. Alveolar macrophages, which are the primary defense against bacterial infection of the lungs, engulf the bacteria; however, *Legionella* is a facultative intracellular parasite and multiplies freely in macrophages . The bacteria bind to alveolar macrophages via the complement receptors and are engulfed into a phagosomal vacuole. However, by an unknown mechanism, the bacteria block the fusion of lysosomes with the phagosome, preventing the normal acidification of the phagolysosome and keeping the toxic myeloperoxidase system segregated from the susceptible bacteria. The bacilli multiply within the phagosome. Eventually, the cell is destroyed, releasing a new generation of microbes to infect other cells.

Bacterial culture, FA tests and DNA probes are used for laboratory diagnosis.

The treatment of choice is erythromycin.

Other Bacterial Pneumonias

Gram positive bacteria that cause pneumonia include *S. aureus* and *S. pyogenes*.

Gram-negative bacteria that cause pneumonia include *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Branhamella catarrhalis*, and *Enterobacter* species.

Klebsiella pneumonia results in lung abscesses and permanent lung damage; the mortality rate is 85%. The treatment of choice is cephalosporins or gentamicin.

Fungal Diseases of the Lower Respiratory System

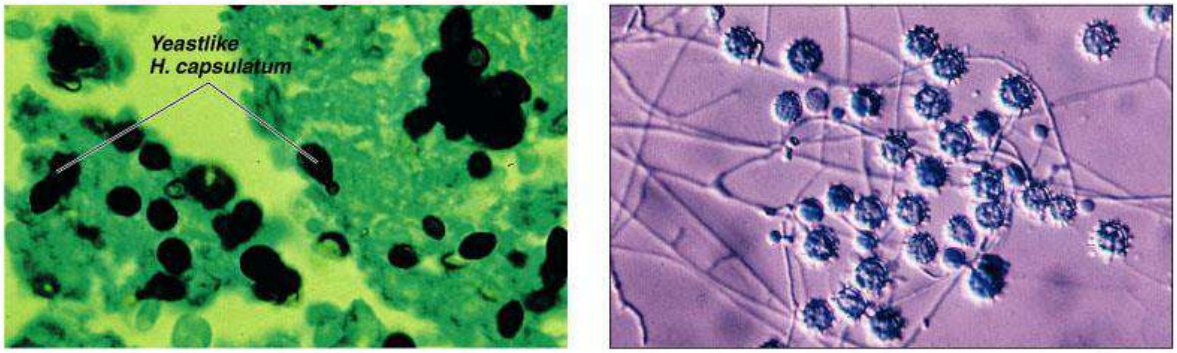
Fungal Diseases are easily inhaled; they may germinate in the lower respiratory tract.

The incidence of fungal diseases has been increasing in recent years.

The mycoses below can be treated with amphotericin B.

Histoplasmosis

Histoplasma capsulatum causes a subclinical infection that only occasionally progresses to a severe, generalized disease. The disease is acquired by inhalation of airborne conidia. Isolation of the fungus or identification of the fungus in tissue samples is necessary for diagnosis.



(a) Yeastlike form typical of growth in tissue at 37°C. Notice that one cell near the center is budding.

(b) Filamentous, spore-forming phase found in soil or at temperatures below 35°C; the spores are usually the infectious particle.

Histoplasma capsulatum

Pneumocystis pneumonia

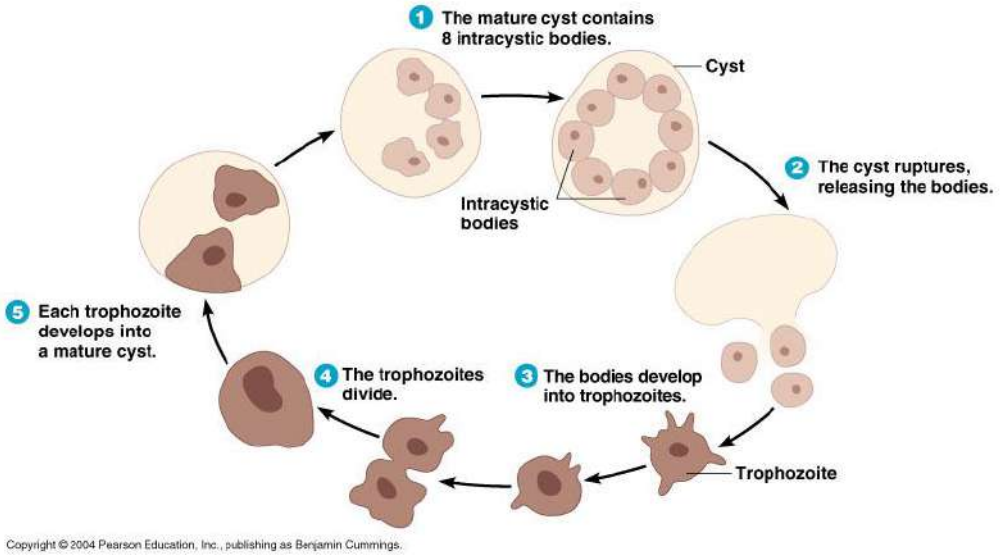
Caused by *Pneumocystis jiroveci* (*carinii*).

Pneumocystis jiroveci is an opportunistic pathogen that invades immunosuppressed or cancer patients.

The life cycle of organism is not well known.

Drug of choice: Trimethoprim-sulfamethoxazole Untreated causes are usually fatal.

Life Cycle of *Pneumocystis jiroveci*



Cyst stage of *Pneumocystis jiroveci* in alveolus of a monkey lung

Other Fungi Involved in Respiratory Disease
Occurs most often in immunosuppressed hosts.
Common causes: Aspergillus , Rhizopus & Mucor

Lect 9

Genitourinary Tract Infections

- Urinary Tract Infections

The urinary system is protected from infection by a number of mechanisms. Sphincter muscles near the urethra keep the system closed most of the time and help prevent infections by stopping bacteria from ascending to the bladder. The downward flow of urine also helps clean the system by washing away microorganisms before they have a chance to multiply and cause infection. In addition, normal urine contains organic acids that may make it acidic, as well as antimicrobial substances such as antibodies. The length and position of the urethra also play a role in preventing infection. Women have a relatively short urethra and because of this they get UTIs far more frequently than men.

Urinary tract infections (UTIs) are considered to be the most common infections in humans. The development of UTIs depends on anatomical factors, the integrity of host defense mechanisms, and the virulence of the infecting organisms. UTIs are classified into disease categories according to the site of infection: cystitis (the bladder), pyelonephritis (the kidney) and bacteriuria (the urine). Successful establishment of infection by bacterial pathogens requires adhesion to host cells, colonization of tissues, and, in certain cases, cellular invasion, followed by intracellular multiplication, dissemination to other tissues, or persistence. Colonization of the urine in the absence of the clinical symptoms is called

asymptomatic bacteriuria (ABU). Most patients with ABU do not need treatment, and in many cases the colonizing by the ABU strains may help to prevent infection by other more virulent bacteria, the reason why ABU patients do not develop symptoms is not properly understood. However, it has been explained by a number of observations that many ABU strains are non adherent and non haemolytic. The strain E. coli 83972, which was isolated from a patient with ABU who had carried it for 3 years, has lost the ability to express functional P and type 1 fimbriae and has, therefore, been able to persist without triggering the host immune response. In contrast to the microorganisms that have acquired genes encoding adhesins for pathogenesis, E. coli 83972 is adapted to commensalism through gene loss and mutation .

The primary causative agents responsible for more than 80% of all UTIs, including both ABU and symptomatic UTIs, are strains of uropathogenic E. coli.

- Routes of infection

In healthy patients most uropathogens originate from rectal flora and enter the urinary tract via the urethra into the bladder . This is known as the ascending route and uropathogens initially adhere to and colonize urothelium of the distal urethra (Fig.1).

Bacteria that reach the renal pelvis can penetrate the renal Parenchyma through the collecting ducts and disrupt the renal tubules. In healthy individuals infection of the kidney through the haematogenous route is uncommon. Occasionally, the renal parenchyma may be breeched in patients with *Staphylococcus aureus* bacteraemia or *Candida* fungaemia that originate from oral sources in immunosuppressed patients . On rare occasions bacteria from adjacent organs may penetrate the urinary tract via the lymphatics. Conditions associated with the lymphatic route are retroperitoneal abscesses and severe bowel infections.

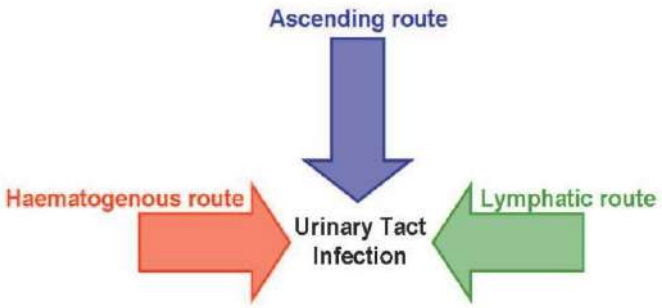


Fig. 1. Urinary tract infections may arise from ascending, haematogenous or lymphatic routes. Ascending routes of infection are most common among patients with an established UTI.

Clinically, UTIs are categorized as uncomplicated or complicated. Uncomplicated UTIs typically affect individuals who are otherwise healthy and have no structural or neurological urinary tract abnormalities; these infections are differentiated into lower UTIs (cystitis) and upper UTIs (pyelonephritis).

Several risk factors are associated with cystitis, including female gender, a prior UTI, sexual activity, vaginal infection, diabetes, obesity and genetic susceptibility. Complicated UTIs are defined as UTIs associated with factors that compromise the urinary tract or host defence, including urinary obstruction, urinary retention caused by neurological disease, immunosuppression, renal failure, renal transplantation, pregnancy and the presence of foreign bodies such as calculi, indwelling catheters or other drainage devices. In the United States, 70–80% of complicated UTIs are attributable to indwelling catheters, accounting for 1 million cases per year. Catheter-associated UTIs (CAUTIs) are associated with increased morbidity and mortality, and are collectively the most common cause of secondary bloodstream infections. Risk factors for developing a CAUTI include prolonged catheterization, female gender, older age and diabetes.

The most common causative agent for both uncomplicated and complicated UTIs is uropathogenic *Escherichia coli* (UPEC). For the agents involved in uncomplicated UTIs, UPEC is followed in prevalence by *Klebsiella pneumonia* , *S. saprophyticus* , *Enterococcus faecalis*, group B *Streptococcus* (GBS) , *Proteus mirabilis* , *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida* spp. For complicated UTIs, the order of prevalence for causative agents, following UPEC as most common, is *Enterococcus* spp., *K. pneumoniae*, *Candida* spp., *S. aureus*, *P. mirabilis*, *P. aeruginosa* and GBS.

Cystitis

Cystitis (inflammation of the bladder) is the most common type of UTI. Bacterial cystitis is common among otherwise healthy women, and is also a frequent healthcare-associated infection.

Bacterial cystitis is sometimes asymptomatic, especially among children and the elderly. When symptoms do occur, they typically start suddenly and include a burning pain during urination (**dysuria**), an urgent need to urinate, and frequent release of small amounts of urine. The urine is cloudy due to accumulation of leukocytes, and may be a pale red color due to blood. It also often has a bad smell. The area above the pubic bone may be painful because of the underlying inflamed bladder. Sometimes a more serious condition called **pyelonephritis**.(infection of the kidneys) develops. Repeated episodes of pyelonephritis lead to scarring and shrinkage of the kidneys and can cause kidney failure.

Causative Agents

Bladder infections usually originate from the normal intestinal microbiota. More than 80% of cases are caused by specific uropathogenic strains of *Escherichia coli.* The remaining infections in young women are caused by other Enterobacteriaceae members such as Gram-negative *Klebsiella* and *Proteus* species, or by Gram-positive *Staphylococcus saprophyticus.* Hospitalized patients, and people with long-standing bladder **catheters** (tubes inserted into the bladder), are often chronically infected with multiple species of bacteria, such as Gram negative *Serratia marcescens* and *Pseudomonas aeruginosa* and Grampositive *Enterococcus faecalis.* Many of these species are resistant to antibiotics and are difficult to treat.

Pyelonephritis

Acute pyelonephritis is a sudden and severe kidney infection. It causes the kidneys to swell and may permanently damage them. Pyelonephritis can be life-threatening.

When repeated or persistent attacks occur, the condition is called chronic pyelonephritis. The chronic form is rare, but it happens more often in children or people with urinary obstructions.

Symptoms usually appear within two days of infection. Common symptoms include:

- a fever greater than (38.9°C)
- pain in the abdomen, back, side, or groin
- painful or burning urination
- cloudy urine
- pus or blood in the urine
- urgent or frequent urination
- fishy-smelling urine

Other symptoms can include:

- shaking or chills
- nausea
- vomiting
- general aching or ill feeling
- fatigue
- mental confusion

Symptoms may be different in children and older adults than they are in other people. For example, mental confusion is common in older adults and is often their only symptom.

People with chronic pyelonephritis may experience only mild symptoms or may even lack noticeable symptoms ..

What are the causes?

The infection usually starts in the lower urinary tract as a urinary tract infection (UTI). Bacteria enter the body through the urethra and begin to multiply and spread up to the bladder. From there, the bacteria travel through the ureters to the kidneys.

Bacteria such as *E. coli* often cause the infection. However, any serious infection in the bloodstream can also spread to the kidneys and cause acute pyelonephritis

UTI pathogenesis

The symptomatic strains of uropathogen , which colonize the urinary tract, may ascend towards bladder to cause cystitis, which is usually associated with the classic symptoms of UTIs. However, UTIs can proceed from the bladder, via the ureters to the kidney, to cause pyelonephritis with the possibility of causing irreversible kidney damage and death. Specific Virulence factors residing on the uropathogen's membrane are responsible for bacterial resistance to the normally effective defence mechanisms of the host.

Adherence is a key event initiating each step in UTI pathogenesis. A UTI typically starts with periurethral contamination by a uropathogen residing in the gut, followed by colonization of the urethra and subsequent migration of the pathogen to the bladder, an event that requires appendages such as flagella and pili . In the bladder, the consequences of complex host–pathogen interactions determine whether uropathogens are successful in colonization or eliminated.

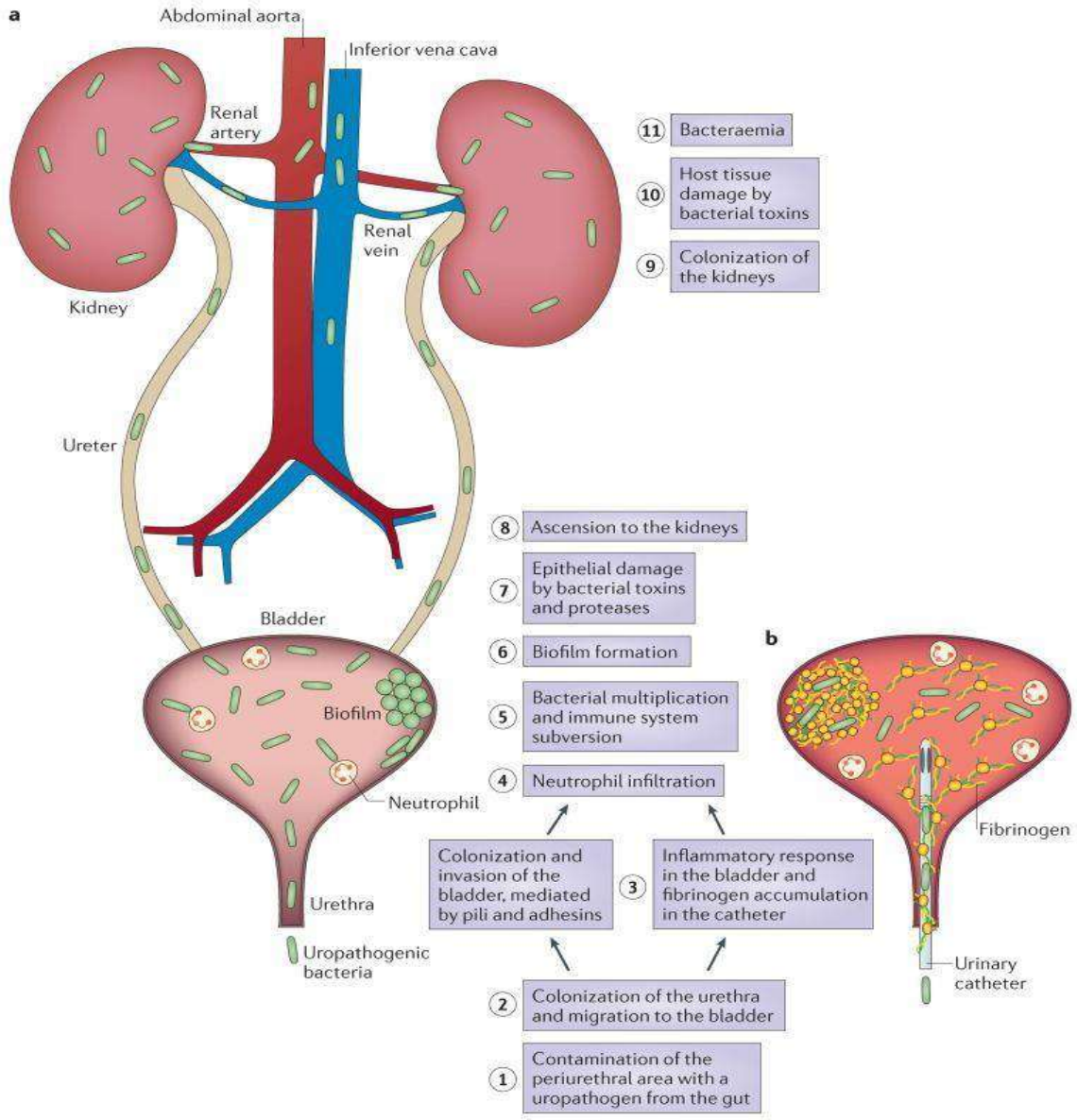


Fig 2 : Pathogenesis of urinary tract infections a | Uncomplicated urinary tract infections (UTIs) begin when uropathogens that reside in the gut contaminate the periurethral area (step 1) and are able to colonize the urethra. Subsequent migration to the bladder (step 2) and expression of pili and adhesins results in colonization and invasion of the superficial umbrella cells (step 3). Host inflammatory responses, including neutrophil infiltration (step 4), begin to clear extracellular bacteria. Some bacteria evade the immune system, either through host cell invasion or through morphological changes that result in resistance to neutrophils, and these bacteria undergo multiplication (step 5) and biofilm formation (step 6). These bacteria produce toxins and proteases that induce host cell damage (step 7), releasing essential nutrients that promote bacterial survival and ascension to the kidneys (step 8). Kidney colonization (step 9) results in bacterial toxin production and host tissue damage (step 10). If left untreated, UTIs can ultimately progress to bacteraemia if the pathogen crosses the tubular epithelial barrier in the kidneys (step 11).

b | Uropathogens that cause complicated UTIs follow the same initial steps as those described for uncomplicated infections, including periurethral colonization (step 1), progression to the urethra and migration to the bladder (step 2). However, in order for the pathogens to cause infection, the bladder must be compromised. The most common cause of a compromised bladder is catheterization. Owing to the robust immune response induced by catheterization (step 3), fibrinogen accumulates on the catheter, providing an ideal environment for the attachment of uropathogens that express fibrinogen-binding proteins. Infection induces neutrophil infiltration (step 4), but after their initial attachment to the fibrinogen-coated catheters, the bacteria multiply (step 5), form biofilms (step 6), promote epithelial damage (step 7) and can seed infection of the kidneys (steps 8 and 9), where toxin production induces tissue damage (step 10). If left untreated, uropathogens that cause complicated UTIs can also progress to bacteraemia by crossing the tubular epithelial cell barrier (step 11).

Multiple bacterial adhesins recognize receptors on the bladder epithelium (also known as the uroepithelium) and mediate colonization. Uropathogens such as UPEC survive by invading the bladder epithelium, producing toxins and proteases to release nutrients from the host cells, and synthesizing siderophores to obtain iron. By multiplying and overcoming host immune surveillance, the uropathogens can subsequently ascend to the kidneys, again attaching via adhesins or pili to colonize the renal epithelium and then producing tissuedamaging toxins. Consequently, the uropathogens are able to cross the tubular epithelial barrier to access the blood stream, initiating bacteraemia.

The uropathogens that cause uncomplicated UTIs, including UPEC, *K. pneumoniae* and *S. saprophyticus*, have the ability to bind directly to the bladder epithelium, which is composed of the umbrella cells (also known as superficial facet cells), intermediate cells and basal cells. UPEC and *K. pneumoniae* bind to uroplakins, which are the major protein components of the umbrella cell apical membrane and which form a crystalline array protecting the mammalian bladder tissue from damaging agents in urine. In addition to uroplakins, $\alpha_3\beta_1$ integrins, which are expressed at the surface of uroepithelial cells, can also serve as receptors for UPEC. By contrast, complicated UTIs are initiated when the bacteria bind to a urinary catheter, a kidney stone or a bladder stone, or when they are retained in the urinary tract by a physical obstruction. Some pathogens (for example, UPEC) can cause both uncomplicated and complicated UTIs. However, others such as *P. mirabilis*, *P. aeruginosa* and *Enterococcus* spp. predominantly cause complicated UTIs. Subsequently, these uropathogens often form biofilms that are responsible for colonization and persistence.

UPEC strains encode a number of virulence factors, which enable the bacteria to colonize the urinary tract and persist in face of highly effective host defense. UPEC

isolates exhibit a high degree of genetic diversity due to the possession of specialized virulence genes located on mobile genetic elements called pathogenicity islands.

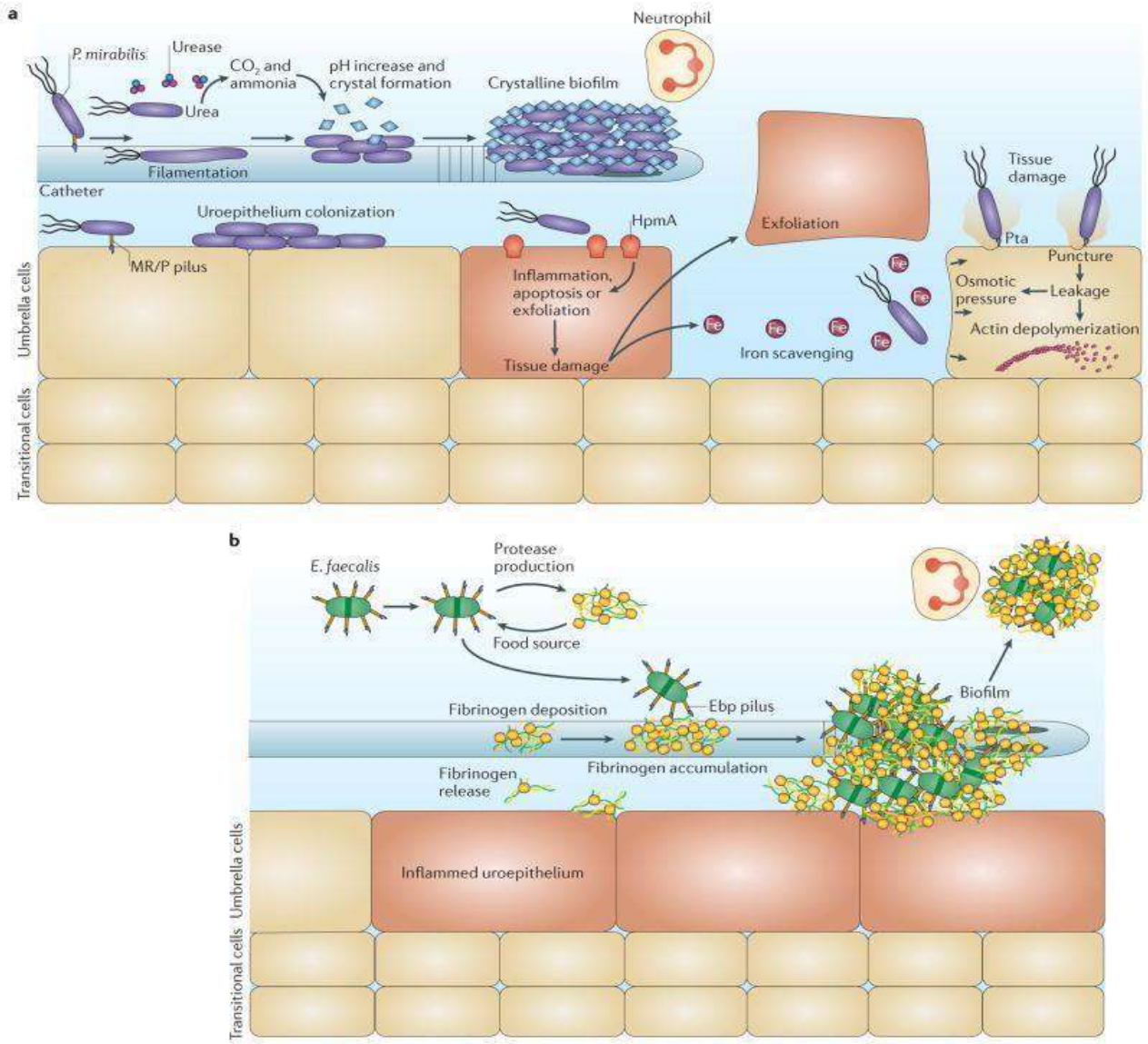
Virulence factors of E. coli that have been potentially implicated as important to establish UTIs can be divided into two groups:

(i) virulence factors associated with the surface of bacterial cell and

(ii) virulence factors, which are secreted and exported to the site of action.

Pathogenesis of *Proteus mirabilis*

Proteus mirabilis produces urease, which hydrolyses urea to carbon dioxide and ammonia. This increases the urine pH and generates calcium crystals and magnesium ammonium phosphate precipitates, which are incorporated into polysaccharide capsules, forming crystalline biofilms on the catheter. The phosphotransferase regulator of swarming behaviour (RsbA) upregulates polysaccharide expression, represses swarming and enhances biofilm formation. Mannose-resistant *Proteus*-like (MR/P) pili intimately associate with the crystal layers, promoting biofilm formation. Oxygen limitation in the biofilm activates the expression of MR/P pili by inducing the recombinase MrpI to reorient the promoter of the pilus genes. Similarly, expression of the fimbrial operon regulator MrpJ leads to decreased motility, promoting biofilm formation.



Mechanisms of pathogenesis during catheter-associated urinary tract infections a | Catheter-associated urinary tract infections (CAUTIs) mediated by *Proteus mirabilis* depend on the expression of mannose-resistant *Proteus*-like (MR/P) pili forinitial attachment, and for biofilm formation on the catheter and in the bladder. Subsequent urease production induces the formation of calcium crystals and magnesium ammonium phosphate precipitates in the urine through the hydrolysis of urea to carbon dioxide and ammonia, resulting in a high pH. The production of extracellular polymeric substances by bacteria attached to the catheter traps these crystals, allowing the formation of a crystalline biofilm, which protects the community from the host immune system and from antibiotics. In addition, these structures prevent proper urine drainage, resulting in reflux and promoting the progression to pyelonephritis, septicaemia and shock. Finally, production of the bacterial toxins haemolysin (HpmA) and *Proteus* toxic agglutinin (Pta) is

important for tissue destruction and bacterial dissemination to the kidneys. HpmA induces pore formation by inserting itself into the cell membrane and destabilizing the host cell, causing tissue damage, exfoliation and nutrient release. Pta punctures the host cell membrane, causing cytosol leakage and resulting in osmotic stress and depolymerization of actin filaments, thus compromising the structural integrity of the cell. The release of nutrients via these toxins also allows the bacteria to scavenge iron using siderophores. b | *Enterococcus faecalis* pathogenesis during CAUTIs depends on catheter implantation, which results in bladder inflammation and causes fibrinogen release, deposition onto the catheter, and accumulation. *E. faecalis* takes advantage of the presence of fibrinogen and uses it as a food source through the production of proteases. *E. faecalis* also binds fibrinogen through the endocarditis- and biofilm-associated (Ebp) pilus, allowing the formation of biofilms that protect the bacteria against the immune system.

Host Factors In Urinary Tract Infection

The host employs several defense mechanisms to eliminate pathogenic and nonpathogenic microorganisms that gain access to the bladder. Factors favoring bacterial elimination include high urine flow rate, high voiding frequency, bactericidal effects of bladder mucosa, secreted proteins that bind to fimbrial adhesins on the bacterial wall, and the inflammatory response mediated by PMNs and cytokines.

In young women, on the other hand, several factors predispose to infection, and these include: 1) short urethra; 2) sexual intercourse ; 3) diaphragm use (manipulation involved in placing it on the cervix may promote bacterial colonization); and 4) spermicide use (raises vaginal pH and is toxic to the normal flora, especially the lactobacilli; it also increases adherence of E.coli to vaginal epithelial cells). Estrogen deficiency has been recognized as a risk factor for recurrent UTIs in postmenopausal women because of ensuing vaginal flora changes: protective lactobacilli are replaced by E.coli and other uropathogens. There may also be genetic factors predisposing young women to UTIs. Women who are of P1 blood group have epithelial cell receptors that mediate attachment of bacteria. 97% of young women with recurrent pyelonephritis are P1 positive, significantly higher than in uninfected controls. Interestingly, patients who had upper tract disease secondary to ureteral reflux had P1 phenotype frequency similar to that in the general population. This highlights the major importance of structural changes in urinary-tract infection. Urinary obstruction, reflux, or other anatomic changes make it possible for less virulent bacteria to produce a urinary tract infection.

Urinary yeast infection left 10

Candida species are the most common cause of fungal urinary tract infections (UTIs). *Candida* UTIs can occur in the lower portion of the urinary tract or in some cases can ascend up to the kidneys.

The following can put you at risk of developing a *Candida* UTI:

- having taken a course of antibiotics
- having a medical device inserted, such as a urinary catheter
- diabetes
- a weakened immune system

Symptoms

Many people with a *Candida* UTI don't have symptoms. If symptoms are present, they can include:

- an increased need to urinate
- a painful or burning sensation when urinating
- abdominal or pelvic pain
- blood in your urine

Genital yeast infection

Candida albicans is the most common cause of genital yeast infections.

Normally, a type of bacteria called *Lactobacillus* keeps the amount of *Candida* in the genital area under control. However, when *Lactobacillus* levels are disrupted in some way, *Candida* can overgrow and cause an infection.

You can also develop a *Candida* genital infection after participating in certain sexual activities, particularly those that involve oral-genital contact.

Although otherwise healthy individuals can get genital *Candida* infections, the following groups are at an increased risk:

- people that have taken antibiotics recently
- people with uncontrolled diabetes
- immunosuppressed individuals
- pregnant women
- people that are taking oral contraceptives or who are on hormone therapy

Symptoms

Symptoms of a genital *Candida* infection can include:

- a burning feeling while having sex or while urinating
- an itchy or painful feeling in or around the vagina
- redness, irritation, or swelling around the vagina
- abnormal vaginal discharge that can be either watery, or thick and white
- a rash around the vagina
- a rash on the penis

Candida species can also infect the male genitals, often if their partner has a vaginal *Candida* infection. The infection may be asymptomatic, but can cause an itchy or burning rash around the head of the penis.